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Stereoselective synthesis of α-substituted serines from protected erythrulose oximes

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Abstract

The additions of organolithium reagents to the C=N bond of several chiral oxime ethers derived from erythrulose afforded protected amino polyols with high diastereoselectivity. Four of the latter compounds have been converted into the α,α-disubstituted α-amino acids (*R*)-2-(−)-methylserine, (*S*)-2-(+)-methylserine, (*R*)-(+)-2-phenylserine and (*R*)-(−)-2-*n*-butylserine.

1. Introduction

Amino polyols[1] and non-proteinaceous amino acids[2] are two types of nitrogen-containing compounds of particular biological relevance. The latter are secondary metabolites occurring in many living organisms[3] and also constitute part of the structure of many peptidic antibiotics.[4] Furthermore, they are used for the synthesis of modified peptides, which display useful properties as enzyme inhibitors and peptidomimetics.[5] Among the non-proteinaceous amino acids, α,α-disubstituted α-amino carboxylic acids, which contain a nitrogen bound to a quaternary carbon atom, have attracted particular interest.[6] Peptides which incorporate this type of amino acid are characterized by a higher conformational rigidity and by an enhanced stability towards hydrolysis.[6–8] There are not many methods of preparing such compounds in enantiopure form. Most of them rely on the alkylation of chiral amino acid enolate equivalents.[9] This fact places some limits on their applicability, as certain α-amino acids, such as those with α-*tert*-alkyl or α-aryl substituents, cannot be easily prepared in this way. Other methods include aldol reactions with amino ester enolates,[10] stereoselective rearrangements,[11] ring-opening of suitably substituted β-lactams,[7g,12] enzymatic resolutions,[13] etc. Very few procedures, aside from the Strecker reaction and its variants,[14] rely on stereoselective additions of carbon nucleophiles to C=N bonds.[15] We have shown that the additions of organolithium reagents to chiral ketoxime ethers (*E*)/(*Z*)-**2**

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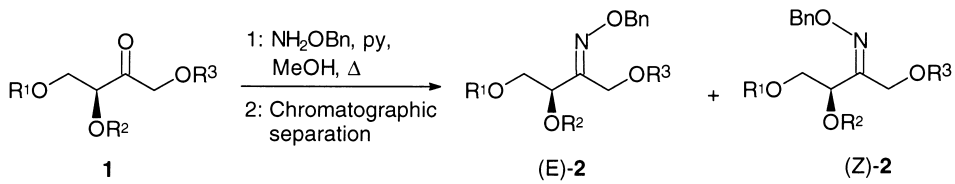
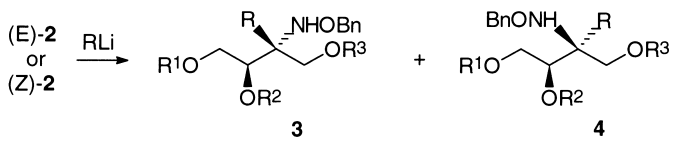
(R^1–R^3=protecting groups) prepared from L-erythrulose derivatives of general formula **1** (Eq. 1), often take place with high stereocontrol to yield the diastereoisomeric, differentially protected amino polyols **3** and/or **4** (Eq. 2).[16] These amino alcohols can then be converted through standard synthetic manipulations into enantiopure amino polyols and α,α-disubstituted α-amino acids, including those not easily available by previous methodologies. In the present paper, we describe in full the preparation of the α,α-disubstituted α-amino acids (*R*)-2-(−)-methylserine, (*S*)-2-(+)-methylserine, (*R*)-(+)-2-phenylserine and (*R*)-(−)-2-*n*-butylserine by means of this methodology.

2. Results and discussion

The starting materials were protected amino polyols **3** (R=Me, *n*Bu, Ph) obtained with a high diastereoisomeric ratio (d.r. >95:5) by addition of the corresponding organolithium reagents to oximes (*E*)-**2**.[16]

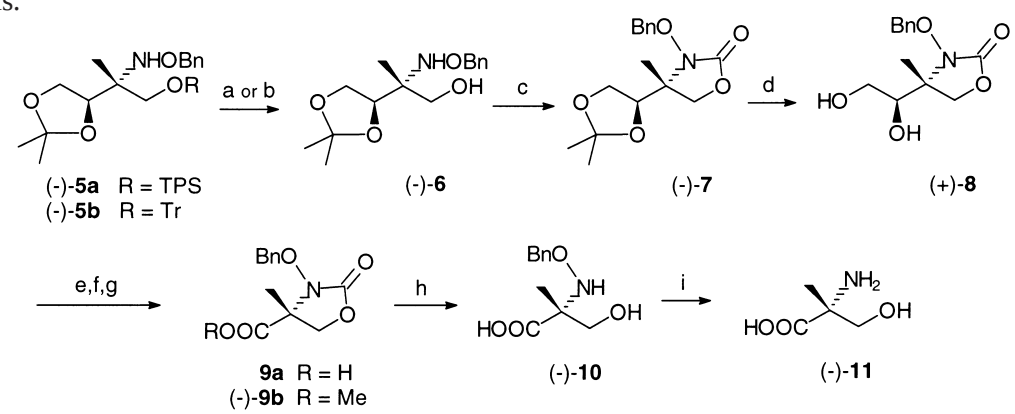


(1)



(2)

Various protecting groups R^1–R^3 have been used for this purpose. Amino polyol acetonides **3** (R^1, R^2=acetonide and R^3=*tert*-butyldiphenylsilyl, TPS, or trityl, Tr) with R=Me, *n*Bu and Ph, obtained with a high d.r. from the appropriate oximes (*E*)-**2**,[16] were selected for transformation into α-substituted serines.[17] In the case of (*R*)-2-(−)-methylserine, for instance, compounds (−)-**5a**/(−)-**5b** were the starting materials.

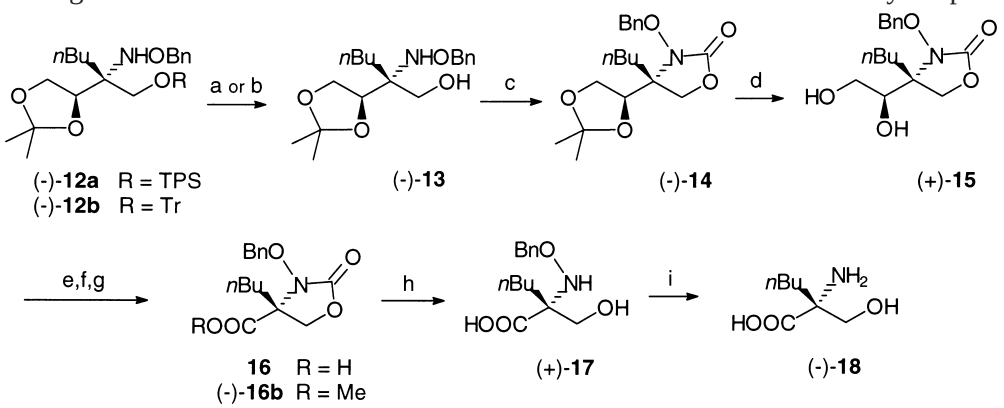


Reaction conditions. a) TBAF, THF, RT. b) TFA/TFAA, CH_2Cl_2, RT. c) CDI, C_6H_6, Δ. d) PPTS, aq MeOH, Δ. e) $NaIO_4$, aq THF, RT. f) $NaClO_2$, NaH_2PO_4, aq *t*BuOH. g) CH_2N_2. h) 2M NaOH, aq EtOH. i) H_2, Pd/C, MeOH.

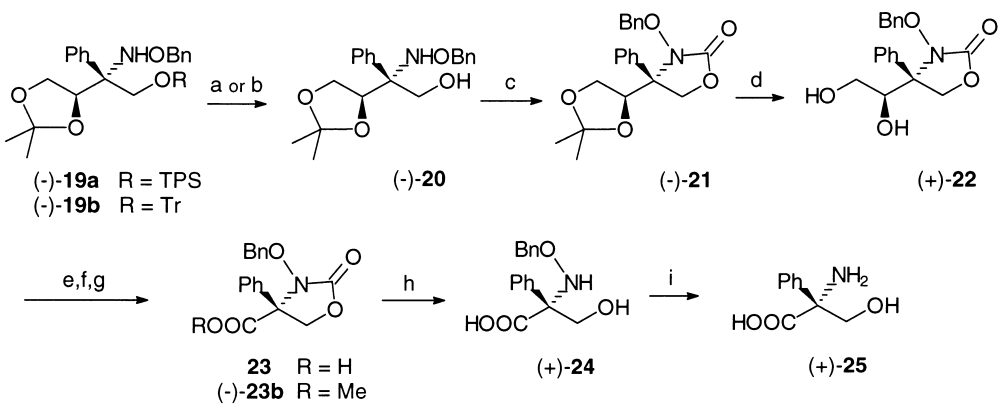
Desilylation of (−)-**5a**, as well as detritylation of (−)-**5b**, provided the protected amino polyol (−)-**6**,[16b] which still contained a small amount of the minor stereoisomer. Treatment of the latter with carbonyldiimidazole (CDI) afforded oxazolidinone (−)-**7** and its minor stereoisomer, which could now be separated by chromatography on silica gel. Acetonide cleavage catalyzed by pyridinium *p*-

toluenesulphonate (PPTS) gave diol (+)-**8**, which was then oxidized via a two-step procedure[18] to acid **9a**, isolated and purified as the methyl ester (−)-**9b**. Basic hydrolysis removed both the oxazolidinone and methyl ester groups and furnished N-benzyloxy amino acid (−)-**10**. Reductive cleavage of the N–O bond was best achieved via hydrogenolysis with a Pd/C catalyst to yield (*R*)-2-methylserine (−)-**11**. Physical and spectral data of the obtained product (see Experimental) were essentially coincident with those reported in the literature.[9a,b,12a,14a]

The amino acids (*R*)-2-*n*-butylserine (−)-**18** and (*R*)-2-phenylserine (+)-**25** were prepared along the same lines as for the synthesis of (−)-**11**. The only difference was the means of cleavage of the acetonide moiety, which was performed by transacetalization with ethanedithiol and *p*-toluenesulphonic acid.[19] The preparation of (*R*)-2-*n*-butylserine has not been previously described in the literature. The amino acid 2-phenylserine has previously been described only in racemic form,[20] although a derivative with unknown configuration was obtained with 67% enantiomeric excess via a metal-catalyzed process.[21]



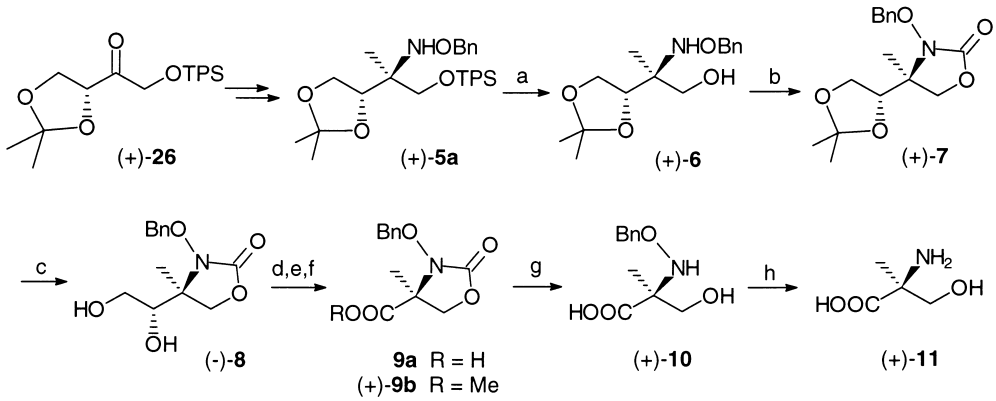
Reaction conditions. a) TBAF, THF, RT. b) TFA/TFAA, CH_2Cl_2, RT. c) CDI, C_6H_6, Δ (85% overall). d) $(CH_2SH)_2$, TsOH, $CHCl_3$, Δ. e) $NaIO_4$, aq THF. f) $NaClO_2$, aq *t*BuOH. g) CH_2N_2 (40% overall). h) aq NaOH/EtOH, RT. i) H_2, Pd/C, MeOH (50% overall).



Reaction conditions. a) TBAF, THF, RT. b) TFA/TFAA, CH_2Cl_2, RT. c) CDI, C_6H_6, Δ (85% overall). d) $(CH_2SH)_2$, TsOH, $CHCl_3$, Δ. e) $NaIO_4$, aq THF. f) $NaClO_2$, aq *t*BuOH. g) CH_2N_2 (40% overall). h) aq NaOH/EtOH, RT. i) H_2, Pd/C, MeOH (50% overall).

The methodology described in this paper does not only allow the synthesis of serine derivatives with the (*R*)-configuration. Their antipodes with the opposite (*S*)-configuration may also be obtained by using D-erythrulose precursors as the starting materials.[22] Therefore, we also synthesized (*S*)-2-methylserine

(+)-**11** from compound (+)-**5a** by the same series of reactions described above for (−)-**11**. Compound (+)-**5a** was in turn prepared in two steps[16b] from the D-erythrulose derivative (+)-**26**.[22]



Reaction conditions. a) TBAF, THF, RT. b) CDI, C_6H_6, Δ (85% overall). c) PPTS, aq MeOH, Δ. d) $NaIO_4$, aq THF. e) $NaClO_2$, aq *t*BuOH. f) CH_2N_2 (40% overall). g) aq NaOH/EtOH, RT. h) H_2, Pd/C, MeOH (50% overall).

The methodology we have described above is therefore very useful for the preparation of many types of α,α-disubstituted α-amino acids in enantiopure form, including those not easily available by alternative procedures. Furthermore, the protected amino polyols obtained with this procedure possess several hydroxyl groups, a fact which opens the way to the synthesis of other biologically relevant, polyfunctionalized compounds, such as polyhydroxylated amino acids,[23] diamino acids,[24] N-hydroxy amino acids,[25] and branched aminosugars.[26] Finally, since D-erythrulose derivatives are also easily available,[22] all these compounds can be prepared in either antipodal form. Further research in these directions is in progress.

3. Experimental

For general experimental details, see the preceeding article.[16b] All obtained products gave satisfactory microanalytical data (C, H, ±0.5%).

3.1. (4R)-3-Benzyloxy-4-methyl-4-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-1,3-oxazolidin-2-one, (−)-7

Amino alcohol (−)-**6**[16b] (1.406 g, 5 mmol) was dissolved in dry benzene (40 ml) and treated with CDI (973 mg, 6 mmol). The reaction mixture was heated at reflux under Ar for 4 h. Work-up (Et_2O) and column chromatography (hexane:EtOAc=4:1) afforded (−)-**7** (1.25 g, 81%) together with its minor diastereomer (100 mg, ca. 6%). Oxazolidinone (−)-**7** was isolated as a white solid, mp 99–100°C, $[\alpha]_D$ −7.2 ($CHCl_3$, *c* 1); IR ν_{max} cm^{-1}: 1782 (C=O); EIMS, *m/z* 307.1411 (M^+). Calcd for $C_{16}H_{21}NO_5$, M=307.1420; ^{1}H NMR: δ 7.45–7.30 (5H, *m*, arom.), 5.01, 4.95 (2H, AB system, J=11 Hz, NOCH_2Ph), 4.31 (1H, *d*, J=8.5 Hz, H-5_a), 4.21 (1H, *dd*, J=7.2, 5.5 Hz, H-4′), 3.96 (1H, *dd*, J=9, 7.2 Hz, H-$5'_a$), 3.86 (1H, *d*, J=8.5 Hz, H-5_b), 3.67 (1H, *dd*, J=9, 5.5 Hz, H-$5'_b$), 1.41, 1.29 (2×3H, 2×*s*, acetonide Me), 0.98 (3H, *s*, MeC_4); ^{13}C NMR: δ 158.5 (C-2), 135.3 (arom. C), 129.9, 128.9, 128.5 (arom. CH), 109.8 (acetonide C), 78.6 (NOCH_2Ph), 76.0 (C-4′), 68.8 (C-5), 68.4 (C-5′), 63.4 (C-4), 25.9, 24.3 (2×acetonide Me), 17.1 (*Me*C_4). Primed numbers in NMR data correspond to atoms of the dioxolane ring. Anal. calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.63; H, 7.00; N, 4.31.

3.2. (4S)-3-Benzyloxy-4-methyl-4-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-1,3-oxazolidin-2-one, (+)-7

Obtained from amino alcohol (+)-**6**[16b] under the same conditions as for (−)-**7**: $[\alpha]_D$ +7 ($CHCl_3$, *c* 1.8). The other physical properties are identical to those of (−)-**7**. Anal. calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.75; H, 6.96; N, 4.44.

3.3. (4R)-3-Benzyloxy-4-methyl-4-[(1R)-1,2-dihydroxyethyl]-1,3-oxazolidin-2-one, (+)-8

Oxazolidinone (−)-**7** (1.23 g, 4 mmol) and PPTS (50 mg, 0.2 mmol) were dissolved in a 9:1 MeOH:H_2O mixture (20 ml) and heated at reflux for 12 h. Work-up[16b] and column chromatography (hexane:EtOAc=1:1) afforded (+)-**8** (987 mg, 92%) as a white solid, mp 118–120°C, $[\alpha]_D$ +17.4 (MeOH, *c* 2.7); IR ν_{max} cm^{-1}: 3400 (br, OH), 1764 (C=O); FABMS, *m/z* 268.1183 ($M+H^+$). Calcd for $C_{13}H_{18}NO_5$, M=268.1185; ^{1}H NMR: δ 7.45–7.30 (5H, *m*, arom.), 5.04, 4.95 (2H, AB system, J=11 Hz, NOC*H*$_2$Ph), 4.43 (1H, *d*, J=8.8 Hz, H-5), 3.86 (1H, *d*, J=8.8 Hz, H-5′), 3.65–3.40 (3H, *m*, C*H*$_2$OHC*H*OH), 2.50 (2H, *br s*, 2 OH), 1.15 (3H, *s*, MeC_4); ^{13}C NMR: δ 159.4 (C-2), 135.3 (arom. C), 130.0, 129.3, 128.8 (arom. CH), 77.9 (NO*C*H$_2$Ph), 71.6 (CHOH), 68.5 (C-5), 65.7 (C-4), 62.1 (CH_2OH), 18.2 (*Me*C_4). Anal. calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.63; H, 6.60; N, 5.31.

3.4. (4S)-3-Benzyloxy-4-methyl-4-[(1S)-1,2-dihydroxyethyl]-1,3-oxazolidin-2-one, (−)-8

Obtained from oxazolidonone (+)-**7** under the same conditions as for (+)-**8**: $[\alpha]_D$ −16.8 (MeOH, *c* 2.2). The other physical properties are identical to those of (+)-**8**. Anal. calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.55; H, 6.30; N, 5.11.

3.5. (4R)-3-Benzyloxy-4-methyl-4-methoxycarbonyl-1,3-oxazolidin-2-one, (−)-9b

Diol (+)-**8** (962 mg, 3.6 mmol) was dissolved in THF (10 ml) and treated with a solution of $NaIO_4$ (1.54 g, 7.2 mmol) in water (2 ml). The reaction mixture was stirred at room temperature for 2 h. Work-up (EtOAc) afforded an oily material which was dissolved in *t*BuOH (70 ml) and treated successively with 2-methyl-2-butene (20 ml), 25% aqueous $NaClO_2$ (13 ml, ca. 36 mmol) and NaH_2PO_4 (3.8 g). The reaction mixture was stirred at room temperature for 12 h. Work-up (EtOAc) afforded an oily material which was directly esterified with ethereal diazomethane. Solvent removal *in vacuo* and column chromatography (hexane:EtOAc=4:1) provided (−)-**9b** (716 mg, 75% overall) as an oil, $[\alpha]_D$ −9.4 ($CHCl_3$, *c* 1.7); IR ν_{max} cm^{-1}: 1793, 1747 (C=O); EIMS, *m/z* 266.1027 ($M+H^+$, 1), 206 ($M^+-COOMe$, 30), 100 (45), 91 (100). Calcd for $C_{13}H_{16}NO_5$, M=266.1028; ^{1}H NMR: δ 7.45–7.30 (5H, *m*, arom.), 5.06, 4.99 (2H, AB system, J=10.7 Hz, NOC*H*$_2$Ph), 4.31 (1H, *d*, J=9 Hz, H-5), 4.00 (1H, *d*, J=9 Hz, H-5′), 3.77 (3H, *s*, OMe), 1.36 (3H, *s*, MeC_4); ^{13}C NMR: δ 170.4 (ester C=O), 157.9 (C-2), 135.1 (arom. C), 129.8, 128.9, 128.4 (arom. CH), 78.8 (NO*C*H$_2$Ph), 69.5 (C-5), 65.4 (C-4), 53.2 (OMe), 18.3 (*Me*C_4). Anal. calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.59; H, 5.55; N, 5.15.

3.6. (4S)-3-Benzyloxy-4-methyl-4-methoxycarbonyl-1,3-oxazolidin-2-one, (+)-9b

Obtained from diol (−)-**8** under the same conditions as for (−)-**9b**: $[\alpha]_D$ +9.0 ($CHCl_3$, *c* 1.8). The other physical properties are identical to those of (−)-**9b**. Anal. calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.67; H, 5.81; N, 5.35.

3.7. (2R)-3-Hydroxy-2-(N-benzyloxyamino)-2-methylpropionic acid, (−)-**10**

Methyl ester (−)-**9b** (663 mg, 2.5 mmol) was dissolved in EtOH (10 ml) and treated with a 2 M aqueous solution of sodium hydroxide (10 ml). The reaction mixture was stirred at room temperature for 12 h. After this time, most of the EtOH was removed *in vacuo* and the pH of the solution was adjusted to 1 with 5 M aq HCl. Work-up (EtOAc) and column chromatography (EtOAc:MeOH=1:1) provided (−)-**10** (366 mg, 65%) as an oil, $[\alpha]_D$ −5.4 (MeOH, *c* 0.2); IR ν_{max} cm^{-1}: 3300 (br, OH), 1591, 1414 (COO^-); CIMS, *m/z* 194.0815 (M^+-CH_2OH). Calcd for $C_{10}H_{12}NO_3$, M=194.0817; ^1H NMR (CD_3OD): δ 7.40–7.20 (5H, *m*, arom.), 4.70 (2H, *s*, NOC*H*$_2$Ph), 3.75 (1H, *d*, J=10.7 Hz, H-3), 3.63 (1H, *d*, J=10.7 Hz, H-3′), 1.20 (3H, *s*, MeC_2); ^{13}C NMR (CD_3OD): δ 181.0 (C-1), 139.3 (arom. C), 129.3, 129.2, 128.6 (arom. CH), 77.5 (NO*C*H$_2$Ph), 67.4 (C-2), 65.9 (C-3), 19.0 (*Me*C_2). Anal. calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.38; H, 6.56; N, 6.05.

3.8. (2S)-3-Hydroxy-2-(N-benzyloxyamino)-2-methylpropionic acid, (+)-**10**

Obtained from methyl ester (+)-**9b** under the same conditions as for (−)-**10**: $[\alpha]_D$ +5.0 (MeOH, *c* 0.3). The other physical properties are identical to those of (−)-**10**. Anal. calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.87; H, 6.76; N, 6.30.

3.9. (R)-(−)-2-Methyl serine, (−)-**11**

Pd/C catalyst (50 mg) was suspended in MeOH (3 ml) and stirred under an H_2 atmosphere for 10 min. Acid (−)-**10** (225 mg, 1 mmol) dissolved in MeOH (15 ml) was then injected via syringe. The mixture was stirred under the H_2 atmosphere at room temperature for 48 h. After this time, the catalyst was removed by filtration and the solvent was removed *in vacuo*. Aqueous 1 M HCl was added to the residue until pH 1. The solution was then evaporated to dryness and the residue was purified through a Dowex 50WX8-400 column according to the described procedure.[9b] This yielded (*R*)-(−)-2-methyl serine, (−)-**11** (65 mg, 55%) as a white solid, mp 225–230°C (dec.), lit.[9a] mp 240–245°C (dec.), lit.[12a] mp 235–245°C (dec.); $[\alpha]_D$ −6.3 (H_2O, *c* 1.1), lit.[9a] $[\alpha]_D$ −5.8 (H_2O, *c* 0.289), lit.[12a] $[\alpha]_D$ −6.1 (H_2O, *c* 0.9); IR ν_{max} cm^{-1}: 3400 (br, OH), 1650, 1450, 1410, 1380, 1275, 1088, 1050, 880; CIMS, *m/z* 120.0692 ($M+H^+$). Calcd for $C_4H_{10}NO_3$, M=120.0660; ^1H NMR (D_2O): δ 3.95 (1H, *d*, J=12 Hz, H-3), 3.70 (1H, *d*, J=12 Hz, H-3′), 1.45 (3H, *s*, Me-C_2); ^{13}C NMR (D_2O): δ 177.2 (C-1), 66.3 (C-3), 63.1 (C-2), 19.9 (*Me*-C_2).

3.10. (S)-(+)-2-Methyl serine, (+)-**11**

Obtained from acid (+)-**10** under the same conditions as for (−)-**11**: $[\alpha]_D$ +6.1 (H_2O, *c* 0.9). The other physical properties are identical to those of (−)-**11**.

3.11. (4R)-3-Benzyloxy-4-n-butyl-4-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-1,3-oxazolidin-2-one, (−)-**14**

Obtained in 75% yield from amino alcohol (−)-**13**[16b] under the same conditions as for (−)-**7**: white solid, mp 85–87°C, $[\alpha]_D$ −8.5 ($CHCl_3$, *c* 1.2); IR ν_{max} cm^{-1}: 1782 (C=O); CIMS, *m/z* 350.1971 ($M+H^+$). Calcd for $C_{19}H_{28}NO_5$, M=350.1967; ^1H NMR: δ 7.40–7.30 (5H, *m*, arom.), 5.00 (2H, *s*, NOC*H*$_2$Ph), 4.27 (1H, *d*, J=8.8 Hz, H-5$_a$), 4.24 (1H, *dd*, J=7, 6 Hz, H-4′), 4.03 (1H, *d*, J=8.8 Hz,

H-5$_b$), 3.95 (1H, *dd*, J=9, 7 Hz, H-5′$_a$), 3.62 (1H, *dd*, J=9, 6 Hz, H-5′$_b$), 1.60 and 1.30–1.15 (6H, *m*, C*H*$_2$C*H*$_2$C*H*$_2$), 1.43, 1.30 (2×3H, 2×*s*, acetonide Me), 0.85 (3H, *t*, J=7 Hz, MeCH$_2$); ^{13}C NMR: δ 158.4 (C-2), 135.3 (arom. C), 129.3, 128.7, 128.4 (arom. CH), 109.7 (acetonide C), 78.4 (NO*C*H$_2$Ph), 76.4 (C-4′), 65.9, 64.7 (C-5, C-5′), 65.7 (C-4), 30.8 (*C*H$_2$C$_3$H$_7$), 25.9, 24.4 (2×acetonide *Me*), 24.9, 22.9 (*C*H$_2$*C*H$_2$), 13.8 (*Me*CH$_2$). Primed numbers in NMR data correspond to atoms of the dioxolane ring. Anal. calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.40; H, 7.66; N, 4.14.

3.12. (4R)-3-Benzyloxy-4-n-butyl-4-[(1R)-1,2-dihydroxyethyl]-1,3-oxazolidin-2-one, (+)-15

Oxazolidinone (−)-**14** (1.048 g, 3 mmol), 1,2-ethane dithiol (2.5 ml, ca. 30 mmol) and *p*-toluenesulphonic acid monohydrate (19 mg, 0.1 mmol) were dissolved in dry $CHCl_3$ (25 ml) and heated at reflux for 2 h. Work-up (CH_2Cl_2) and column chromatography (hexane:EtOAc=1:1) furnished (+)-**15** (753 mg, 81%) as a white solid, mp 74–76°C, $[\alpha]_D$ +54.4 ($CHCl_3$, *c* 1.7); IR ν_{max} cm^{-1}: 3400 (br, OH), 1765 (C=O); FABMS, *m/z* 310.1642 (M+H$^+$). Calcd for $C_{16}H_{24}NO_5$, M=310.1655; ^{1}H NMR: δ 7.45–7.35 (5H, *m*, arom.), 5.10, 5.00 (2H, AB system, J=11.3 Hz, NOC*H*$_2$Ph), 4.41 (1H, *d*, J=9 Hz, H-5), 3.96 (1H, *d*, J=9 Hz, H-5′), 3.60 (1H, *m*, C*H*$_2$OH), 3.40 (2H, *m*, C*H*$_2$OH, C*H*$_2$OH), 2.30, 2.10 (2H, 2×*br s*, 2×OH), 1.60–1.20 (6H, *m*, C*H*$_2$C*H*$_2$C*H*$_2$), 0.89 (3H, *t*, J=7.2 Hz, Me); ^{13}C NMR: δ 159.6 (C-2), 135.4 (arom. C), 129.8, 129.4, 128.9 (arom. CH), 77.3 (NO*C*H$_2$Ph), 71.8 (CHOH), 67.9 (C-4), 66.7 (C-5), 62.0 (CH$_2$OH), 32.5 (*C*H$_2$C$_3$H$_7$), 24.9, 23.0 (*C*H$_2$*C*H$_2$), 13.9 (Me). Anal. calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.33; H, 7.46; N, 4.34.

3.13. (4R)-3-Benzyloxy-4-n-butyl-4-methoxycarbonyl-1,3-oxazolidin-2-one, (−)-16b

Obtained in 90% yield from diol (+)-**15** under the same conditions as for (−)-**9b**: oil, $[\alpha]_D$ −6.5 ($CHCl_3$, *c* 1.3); IR ν_{max} cm^{-1}: 1790, 1746 (C=O); EIMS, *m/z* 308.1494 (M+H$^+$, 1), 248 (M$^+$–COOMe, 8), 142 (15), 91 (100). Calcd for $C_{16}H_{22}NO_5$, M=308.1498; ^{1}H NMR: δ 7.45–7.35 (5H, *m*, arom.), 5.10, 5.06 (2H, AB system, J=10.3 Hz, NOC*H*$_2$Ph), 4.38 (1H, *d*, J=9 Hz, H-5), 4.16 (1H, *d*, J=9 Hz, H-5′), 3.78 (3H, *s*, OMe), 1.85 (2H, *m*, C*H*$_2$C$_3$H$_7$), 1.30–1.20 (4H, *m*, C*H*$_2$C*H*$_2$), 0.86 (3H, *t*, J=7 Hz, *Me*CH$_2$); ^{13}C NMR: δ 170.4 (ester C=O), 158.0 (C-2), 135.1 (arom. C), 129.5, 128.7, 128.4 (arom. CH), 78.7 (NO*C*H$_2$Ph), 67.9 (C-4), 67.3 (C-5), 53.0 (OMe), 32.1 (*C*H$_2$C$_3$H$_7$), 24.9, 22.7 (*C*H$_2$*C*H$_2$), 13.7 (Me). Anal. calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.43; H, 7.01; N, 4.54.

3.14. (2R)-2-(N-Benzyloxyamino)-2-(hydroxymethyl)hexanoic acid, (+)-17

Obtained in 73% yield from methyl ester (−)-**16b** under the same conditions as for (−)-**10**: white solid, mp 120–125°C (dec.), $[\alpha]_D$ +1.7 ($CHCl_3$, *c* 0.3); IR ν_{max} cm^{-1}: 3300 (br, OH), 1586, 1426, 1264, 1091, 874; FABMS, *m/z* 268.1538 (M+H$^+$). Calcd for $C_{14}H_{22}NO_4$, M=268.1549; ^{1}H NMR (CD_3OD): δ 7.40–7.20 (5H, *m*, arom.), 4.75, 4.71 (2H, AB system, J=11.5 Hz, NOC*H*$_2$Ph), 3.79 (1H, *d*, J=10.7 Hz, C*H*$_2$OH), 3.67 (1H, *d*, J=10.7 Hz, C*H*$_2$OH), 1.55 (2H, *m*, H-3), 1.40–1.20 (4H, *m*, H-4, H-5), 0.87 (3H, *t*, J=7 Hz, H-6); ^{13}C NMR (CD_3OD): δ 180.5 (C-1), 139.0 (arom. C), 129.4, 129.3, 128.8 (arom. CH), 77.5 (NO*C*H$_2$Ph), 70.9 (C-2), 64.2 (CH$_2$OH), 31.6 (C-3), 26.9, 24.3 (C-4, C-5), 14.5 (C-6). Anal. calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.83; H, 7.61; N, 5.46.

3.15. (R)-(−)-2-n-Butyl serine, (−)-18

Obtained in 50% yield from acid (+)-**17** under the same conditions as for (−)-**11**: white solid, mp 225–232°C (dec.); $[\alpha]_D$ −11.8 (H_2O, *c* 0.3); IR ν_{max} cm^{-1}: 3300 (br, OH), 1625, 1449, 1092; FABMS, *m/z* 162.1133 ($M+H^+$). Calcd for $C_7H_{16}NO_3$, M=162.1130; ^1H NMR (D_2O:CD_3OD=4:1): δ 3.90 (1H, *d*, J=11.5 Hz, CH_2OH), 3.66 (1H, *d*, J=11.5 Hz, CH_2OH), 1.80–1.60 (2H, *m*, C$H_2C_3H_7$), 1.50–1.15 (4H, *m*, CH_2CH_2), 0.87 (3H, *t*, J=7 Hz, Me); ^{13}C NMR (D_2O:CD_3OD=4:1): δ 175.6 (C-1), 67.3 (C-2), 65.4 (CH_2OH), 32.9 (C-3), 25.9, 23.0 (C-4, C-5), 13.9 (C-6). Anal. calcd for $C_7H_{15}NO_3$: C, 52.16; H, 9.38; N, 8.69. Found: C, 52.33; H, 9.60; N, 8.56.

3.16. (4R)-3-Benzyloxy-4-phenyl-4-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-1,3-oxazolidin-2-one, (−)-21

Obtained in 93% yield from amino alcohol (−)-**20**[16b] under the same conditions as for (−)-**7**: white solid, mp 90–92°C, $[\alpha]_D$ −36.2 ($CHCl_3$, *c* 1.4); IR ν_{max} cm^{-1}: 1788 (C=O); FABMS, *m/z* 370.1651 ($M+H^+$). Calcd for $C_{21}H_{24}NO_5$, M=370.1655; ^1H NMR: δ 7.40–7.20 (10H, *m*, arom.), 5.07, 4.72 (2H, AB system, J=10.2 Hz, NOCH_2Ph), 4.94 (1H, *dd*, J=7.5, 4.8 Hz, H-4′), 4.67 (1H, *d*, J=9 Hz, H-5_a), 4.44 (1H, *d*, J=9 Hz, H-5_b), 4.12 (1H, *dd*, J=9.3, 7.4 Hz, H-$5'_a$), 3.65 (1H, *dd*, J=9.3, 4.8 Hz, H-$5'_b$), 1.49, 1.35 (2×3H, 2×*s*, acetonide Me); ^{13}C NMR: δ 158.3 (C-2), 136.8, 134.8 (arom. C), 129.3, 128.9, 128.6, 128.3, 126.9 (arom. CH), 110.4 (acetonide C), 78.6 (NO*C*H_2Ph), 74.8 (C-4′), 68.5 (C-5), 68.3 (C-4), 65.4 (C-5′), 25.7, 24.0 (2×acetonide Me). Primed numbers in NMR data correspond to atoms of the dioxolane ring. Anal. calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.39; H, 6.44; N, 3.56.

3.17. (4R)-3-Benzyloxy-4-phenyl-4-[(1R)-1,2-dihydroxyethyl]-1,3-oxazolidin-2-one, (+)-22

Obtained in 66% yield from oxazolidinone (−)-**21** under the same conditions as for (+)-**15**: white solid, mp 68–70°C, $[\alpha]_D$ +24.0 ($CHCl_3$, *c* 0.7); IR ν_{max} cm^{-1}: 3400 (br, OH), 1778 (C=O); CIMS, *m/z* 330.1345 ($M+H^+$). Calcd for $C_{18}H_{20}NO_5$, M=330.1341; ^1H NMR: δ 7.50–7.20 (10H, *m*, arom.), 5.15, 4.87 (2H, AB system, J=10.2 Hz, NOCH_2Ph), 4.44 (1H, *t*, J=4 Hz, C*H*OH), 4.38 (1H, *br d*, J=12 Hz, H-5_a), 4.26 (1H, *br d*, J=12 Hz, H-5_b), 4.00 (2H, *br d*, J=4 Hz, CH_2OH), 3.30 (2H, *br s*, 2 OH); ^{13}C NMR: δ 159.6 (C-2), 137.2, 134.8 (arom. C), 129.2, 129.0, 128.7, 128.6, 128.3, 126.1 (arom. CH), 82.7 (CHOH), 78.4 (NO*C*H_2Ph), 71.3 (C-4), 60.6 (C-5), 58.6 (CH_2OH). Anal. calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.42; H, 5.70; N, 4.44.

3.18. (4R)-3-Benzyloxy-4-phenyl-4-methoxycarbonyl-1,3-oxazolidin-2-one, (−)-23b

Obtained in 61% overall yield from diol (+)-**22** under the same conditions as for (−)-**9b**: oil, $[\alpha]_D$ −17.7 ($CHCl_3$, *c* 1.3); IR ν_{max} cm^{-1}: 1794, 1753 (C=O); EIMS, *m/z* 328.1175 ($M+H^+$, 1), 312 (M^+-Me, 1), 268 ($M^+-COOMe$, 38), 162 (20), 91 (100). Calcd for $C_{18}H_{18}NO_5$, M=328.1185; ^1H NMR: δ 7.40–7.30 (10H, *m*, arom.), 5.19, 5.05 (2H, AB system, J=10 Hz, NOCH_2Ph), 4.71 (1H, *d*, J=9 Hz, H-5), 4.54 (1H, *d*, J=9 Hz, H-5′), 3.86 (3H, *s*, OMe); ^{13}C NMR: δ 169.5 (ester C=O), 157.1 (C-2), 134.8, 134.3 (arom. C), 129.3, 129.0, 128.6, 128.3, 126.5 (arom. CH), 78.9 (NO*C*H_2Ph), 71.1 (C-4), 69.9 (C-5), 53.3 (OMe). Anal. calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 66.22; H, 5.40; N, 4.49.

3.19. (2R)-3-Hydroxy-2-(N-benzyloxyamino)-2-phenylpropionic acid, (+)-**24**

Obtained in 70% yield from methyl ester (−)-**23b** under the same conditions as for (−)-**10**: white solid, mp 144–146°C, $[\alpha]_D$ −12.5 (MeOH, *c* 1.7); IR ν_{max} cm^{-1}: 3300 (br, OH), 1589, 1412, 1091, 913, 874; FABMS, *m/z* 288.1227 ($M+H^+$). Calcd for $C_{16}H_{18}NO_4$, M=288.1236; ^1H NMR (CD_3OD): δ 7.45 (2H, *m*, arom.), 7.30–7.15 (8H, *m*, arom.), 4.61, 4.53 (2H, AB system, J=10.5 Hz, NOCH_2Ph), 4.25 (1H, *d*, J=10.5 Hz, H-3), 4.07 (1H, *d*, J=10.5 Hz, H-3); ^{13}C NMR (CD_3OD): δ 180.5 (C-1), 140.6, 138.8 (arom. C), 129.6, 129.5, 129.3, 129.0, 128.8, 128.7, 128.4 (arom. CH), 77.7 (NOCH_2Ph), 73.8 (C-2), 65.1 (C-3). Anal. calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.72; H, 5.70; N, 4.69.

3.20. (R)-(+)-2-Phenyl serine, (+)-**25**

Obtained in 60% yield from acid (+)-**24** under the same conditions as for (−)-**11**: white solid, mp 248–250°C (dec.); $[\alpha]_D$ +19.5 (H_2O, *c* 0.3); IR ν_{max} cm^{-1}: 3400 (br, OH), 1624, 1407, 1087, 875; FABMS, *m/z* 182.0822 ($M+H^+$). Calcd for $C_9H_{12}NO_3$, M=182.0817; ^1H NMR (D_2O:CD_3OD=4:1): δ 7.55–7.40 (5H, *m*, arom.), 4.35 (1H, *d*, J=12 Hz, H-3), 4.24 (1H, *d*, J=12 Hz, H-3); ^{13}C NMR (D_2O:CD_3OD=4:1): δ 174.3 (C-1), 135.6 (arom. C), 130.3, 130.2, 126.8 (arom. CH), 68.5 (C-2), 64.5 (C-3). Anal. calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.45; H, 6.38; N, 7.58.

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