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A Practical Stereoselective Synthesis of both Enantiomers of *Threo*- and *Erythro*-β-Hydroxy Norvaline from (*S*)-Serine Derivatives

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Abstract—The four enantiopure diastereoisomers of β-hydroxy norvaline have been prepared from l-serine in moderate chemical yield. The method is based on the diastereoselective addition of different organometallics to easily accessible serinal derivatives.

Introduction

The interest in β-hydroxy-α-amino acids, a class of primary metabolites, is based in their biological activity as enzyme inhibitors,[1] and as starting materials in the synthesis of more complex molecules.[2] In recent years the interest in the synthesis of both natural and non-proteinogenic amino acids in enantiopure form has grown and some general methods have been developed.[3] Some stereoselective approaches are based on aldol condensation of aldehydes with glycine derivatives,[4] Sharpless asymmetric epoxidation/dihydroxylation[5] or electrophilic amination of β-hydroxy esters.[6] Stereoselective additions to serine derivatives[7] or stereoselective reductions of α-amino ketones[8] also constitute a good entry to these compounds, although some of these methods allowed the preparation of only one stereoisomer.[9]

We have previously reported[10] that diethylzinc shows a very high *syn* selectivity in additions to chiral α-dibenzylamino aldehydes, and it constitutes an alternative to the use of some other organometallics.[11] In this way (*S*)-*N*,*N*-dibenzyl-O-TBDMS-serinal **1** has been used by us and others[12] as a starting chiron in the stereodivergent synthesis of chiral compounds and sphingosine derivatives[13] by tuning the nature of the organometallic used as nucleophile.

Now we report our efforts on the development of a simple methodology for the control of the relative and absolute stereochemistry of the two stereocenters in the stereodivergent synthesis of β-hydroxy-α-amino acids from serine derivatives taking *threo* and *erythro*-β-hydroxy norvaline as a model.

The first approach started from 2-amino-1,3-diols *syn*-**2** and *anti*-**2** prepared by alkylation of (*S*)-*N*,*N*-dibenzyl-O-TBDMS-serinal in three steps with 73 and 64% overall yield respectively. The key step of this route was the oxidation of the alcohol into the carboxylic group. Attempts to convert amino alcohol derivatives **2** into carboxylic acids **4** by oxidation with PDC failed because a very complex mixture of degradation compounds was formed. Then, the oxidation was achieved in two steps. First, *syn*-**2** and *anti*-**2** were submitted to Swern oxidation affording *syn*- and *anti*-3-hydroxynorvalinals **3** respectively in excellent yield. Searching for an oxidant capable to transform the aldehydes **3** into the carboxylic acids **4** and compatible with the *N*,*N*-dibenzylamino and MEM groups some systems have been tested[14] (Scheme 1).

Treatment of *syn*-**3** with the system $NaIO_4$-RuO_2 at rt[15] led to degradation and the isolation of **7** in 12% yield as only identified product as a consequence of benzylic oxidation and oxidation-elimination of the MEM group. When *syn*-**3** and *anti*-**3** were subjected to reaction with $KMnO_4$ in *t*-BuOH-5% NaH_2PO_4 at 0°C as described by Masamune[16] *syn*-**4** and *anti*-**4** were obtained but in modest yield. The best results in the protected α-amino-β-hydroxy acids **4** was obtained by oxidation of aldehydes **3** with $NaClO_2$/KH_2PO_4/2-methyl-2-butene in *t*BuOH-CH_3CN at 0°C by a modified reported procedure.[17] These conditions allowed reproducible formation of *syn*- and *anti*-**4** in good yield, although accompanied by amides **8** and *ent*-**8**. The formation of this by-product, due to C-C bond cleavage is known to occur for oxidations of enolizable aldehydes.[18]

Deprotection of *syn*- and *anti*-**4** by treatment with 2N

Keywords: diastereoselective synthesis; aminoalcohols; alkylzincs; aminoaldehydes.

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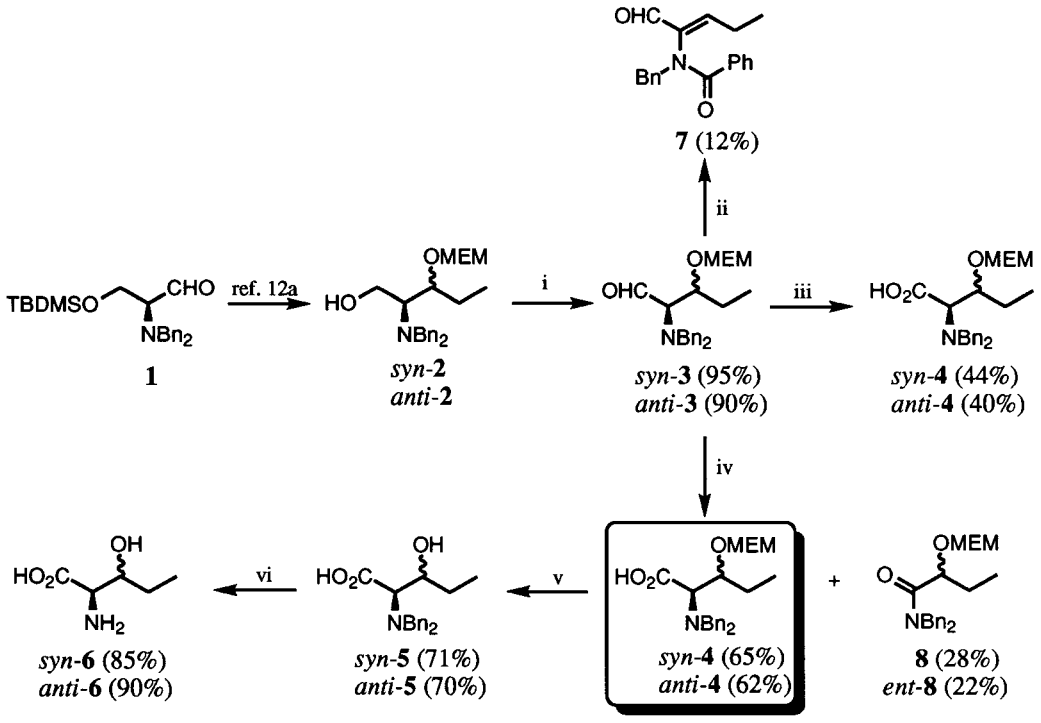


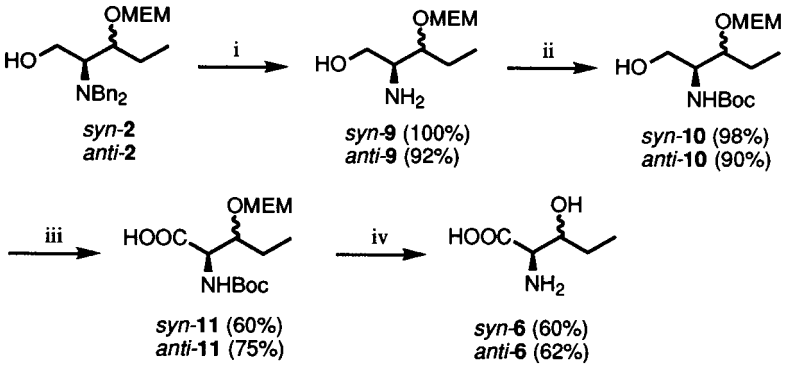
Scheme 1. *Reagents and conditions:* (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C; (ii) $NaIO_4$-RuO_2, $CH_3CN/CCl_4/H_2O/(CH_3)_2CO$, rt; (iii) $KMnO_4$, *t*BuOH-5% NaH_2PO_4, 0°C; (iv) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, CH_3CN-*t*BuOH, 0°C; (v) 2N HCl, THF-H_2O, 20°C for *syn*-**4**; NaI, TMSCl, CH_3CN, −20°C for *anti*-**4**; (vi) H_2, $Pd(OH)_2$-C, MeOH-H_2O.

solution of HCl in THF-H_2O and NaI/TMSCl in acetonitrile at −20°C lead to *syn*- and *anti*-**5**, that were efficiently converted by low pressure hydrogenolysis over $Pd(OH)_2$[19] into the target (2*R*, 3*S*)- and (2*R*, 3*R*)-β-hydroxy-norvaline respectively. The physical and spectroscopic data were coincident with the literature values,[9c,20] and their specific rotations confirmed the stereochemistry and enantiomeric purity of the final compounds.

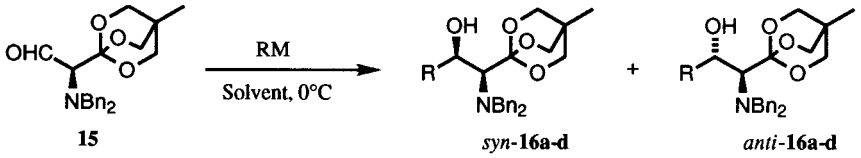
To overcome the problems in the oxidation step associated to the presence of the dibenzylamino moiety, an alternative way to hydroxy norvalines was followed as summarized in Scheme 2.

In this way, the starting *syn*- and *anti*-**2** were debenzylated to *syn*- and *anti*-**9** by hydrogenolysis over $Pd(OH)_2$ and transformed into the *N*-Boc derivatives *syn*- and *anti*-**10** by treatment with Boc_2O. The oxidation of *N*-Boc amino-alcohols by PDC (5 equiv.) in DMF at 20°C yielded the β-hydroxy-α-amino acid derivatives *syn*- and *anti*-**11** in good yields. Finally, removal of the carbamate and MEM groups under acid conditions delivered the desired *syn*- and *anti*-β-hydroxy norvalines **6**.

Since the utility of the commented synthetic ways was limited by the oxidation step of the alcohol to the carboxylic acid an alternative and complementary route was envisaged to obtain β-hydroxy norvalines more directly avoiding the oxidation step. The novel approach is based in masking the carboxylic group of serine as a trioxabicyclo [2.2.2]ortho-ester (OBO)[21] and on the diastereoselective addition of organometallics to serinal derivative **15**.



Scheme 2. *Reagents and conditions:* (i) H_2, $Pd(OH)_2$-C, MeOH; (ii) Boc_2O, CH_2Cl_2, 20°C; (iii) PDC, DMF, 20°C; (iv) 1. 2N HCl, 2. Propylene oxide, EtOH, reflux.



Scheme 3.

Previously the reactions of **15** with different magnesium and zinc derivatives have been tested. Thus, **15** was converted into the *syn* aminoalcohols **16a**–**d** by treatment with an excess (4 equiv.) of dimethyl-, diethyl-, diisopropyl- and diphenylzinc respectively (Scheme 3). As expected, the addition of zinc derivatives proceeded under chelation control[10] leading stereoespecifically to alkyl derivatives **16a**–**c** (entries 2, 4, 6 in Table 1) and with moderate d.e. to the phenyl derivative **16d** (entry 8). In the same way, methylmagnesium iodide, ethylmagnesium bromide, isopropylmagnesium bromide and phenylmagnesium bromide react with **15**, in a non chelation mode, giving *anti*-**16a**–**d** as major diastereoisomers (entries 1, 3, 5 and 7 in Table 1).

Table 1. Reaction of serinal derivative **15** with magnesium and zinc derivatives

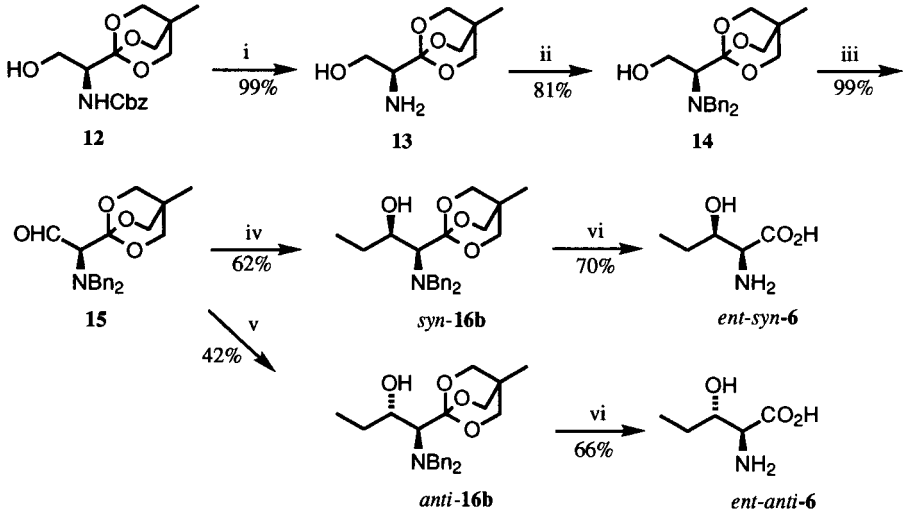
Entry	RM	Solvent	t (H)	Yield (%)[a]	**16** (*syn:anti*)[b]
1	MeMgI	Et_2O	1	48	**16a** (17:83)
2	Me_2Zn	Toluene	144	27[c]	**16a** (100:0)[d]
3	EtMgBr	Et_2O	2	54[e]	**16b** (22:78)
4	Et_2Zn	Toluene-hexane	6	62	**16b** (100:0)[d]
5	*i*-PrMgCl	Et_2O	4[f]	44	**16c** (12:88)
6	*i*-Pr_2Zn	Toluene-hexane	2.5	79	**16c** (100:0)[d]
7	PhMgBr	Et_2O	18	55	**16d** (17:83)
8	Ph_2Zn	Toluene	6	62	**16d** (76:24)

[a] Yields refer to pure and isolated compounds.
[b] Measured by integration of the ^1H NMR signals in the reaction mixture.
[c] Aminoaldehyde **15** was recovered (50%).
[d] Stereoisomers *anti* were not detected in ^1H NMR spectra.
[e] The reduction alcohol (**14**) was also isolated (16%).
[f] The reaction was carried out at −78°C.

The synthesis of β-hydroxy norvalines *ent-syn*-**6** and *ent-anti*-**6** was then envisaged from (*S*)-serine as summarized in Scheme 4.

Cbz-l-Ser-OBO ester **12** was prepared from commercially available Cbz-serine in two steps as previously described,[7f,g] and transformed into **13** by hydrogenolysis on Pearlman's catalyst. Reaction of **13** with benzyl bromide in the presence of potassium carbonate gave **14**, which upon Swern oxidation yielded (*S*)-*N*,*N*-dibenzyl-OBO-serinal **15** in excellent yield. The stereodivergent preparation of diastereomeric *syn*- and *anti*-**16b** was achieved, in moderate chemical yield, by addition of diethylzinc (entry 4 in Table 1) and ethylmagnesium bromide (entry 3 in Table 1) to **15** respectively. Debenzylation by hydrogenolysis, followed by elimination of the OBO protective group by sequential treatment with 2N HCl in THF-H_2O and Na_2CO_3 solution lead to (2*S*, 3*R*)-β-hydroxy norvaline (*ent-syn*-**6**) and (2*S*, 3*S*)-β-hydroxy norvaline (*ent-anti*-**6**).

In summary, the results summarized now show a new stereodivergent synthesis of all the four diastereoisomers of β-hydroxy norvaline from serinal derivatives **1** and **15** readily available from l-serine. Further investigation into the scope and utility of these intermediates for the synthesis of a variety of enantiopure β-hydroxy-α-amino acids is in progress.



Scheme 4. *Reagents and conditions:* (i) H_2, $Pd(OH)_2$-C, MeOH; (ii) BnBr, K_2CO_3, CH_3CN, 20°C; (iii) $(COCl)_2$, DMSO, Et_3N, −78°C; (iv) Et_2Zn, hexane-toluene, 0°C; (v) EtMgBr, Et_2O, 0°C; (vi) 1. H_2, $Pd(OH)_2$-C, MeOH, 2. HCl 2N, THF-H_2O, rt. 3. Na_2CO_3, dioxane-H_2O, then HCl 2N. 4. Propylene oxide, EtOH, reflux.

Experimental

General

The reactions were carried out in oven-dried glassware, under argon atmosphere, and using anhydrous solvents. Starting aminoaldehydes *syn*-**3** and *anti*-**3** were prepared as previously described.[12a] Diethylzinc, as 1 M solution in hexane and dimethylzinc as 2 M solution in toluene, were purchased from Aldrich. Diisopropylzinc and diphenylzinc were prepared from isopropylmagnesium chloride and phenyllithium and $ZnCl_2$ by a described method.[22] The ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were registered on a Bruker AC 300 or Bruker AMX 300, using TMS as internal standard. IR spectra were recorded on a Philips PU 9706 Spectrometer, as film or KBr dispersion. Optical rotations were measured on a Perkin–Elmer 241 Polarimeter in a 1 dm. cell.

(2*R*,3*S*)-2-(*N*,*N*-Dibenzylamino)-3-[(2-methoxyethoxy)-methoxy]-1-pentanoic acid (*syn*-4). *Procedure A* ($KMnO_4$/NaH_2PO_4). A solution of *syn*-**3** (289 mg, 0.75 mmol) in *t*-BuOH (4 mL) was diluted with an aqueous 5% NaH_2PO_4 solution (4 mL) and to the resulting mixture was added, with vigorous stirring, an aqueous 1 M $KMnO_4$ solution (1.5 mmol, 2 equiv.) at 0°C. After 40 min, the reaction was quenched by addition of a saturated solution of Na_2SO_3 and the mixture was adjusted to pH=6 by addition of cold (0°C) 10% HCl. The usual extractive workup with ethyl acetate followed by flash chromatography (silica gel, hexane/EtOAc: 1/2) provided the carboxylic acid *syn*-**4** as a colorless oil: 133 mg (0.33 mmol, 44%). $[\alpha]_D^{23}=+47.4$ (c=0.8, $CHCl_3$). IR (film): 3500–2500, 1700, 1450, 750, 700 cm^{-1}. ^1H NMR ($CDCl_3$): 0.67 (t, 3H, J=7.4 Hz, CH_3CH$_2$); 1.82 (m, 2H, CH$_2$CH$_3$); 3.41 (s, 3H, CH_3O); 3.53 (d, 1H, J=4.7 Hz, C*H*N); 3.60 (m, 3H, OC*H*HCH_2O); 3.81 (m, 1H, OCH*H*CH$_2$O); 3.95 (d, 2H, J=14.0 Hz, C*H*HPh); 4.05 (m, 1H, C*H*OMEM); 4.22 (d, 2H, J=14.0 Hz, CH*H*Ph); 4.72 (d, 1H, J=7.1 Hz, OC*H*HO); 4.76 (d, 1H, J=7.1 Hz, OCH*H*O); 7.20–7.50 (m, 10H, H_{arom}); 7.75 (br s, 1H, CO$_2$*H*). ^{13}C NMR ($CDCl_3$): 9.6 (*C*H$_3$CH$_2$); 24.5 (*C*H$_2$CH$_3$); 55.8 (*C*H$_2$Ph); 58.9 (*C*H$_3$O); 62.8 (*C*HN); 67.1 (O*C*H$_2$CH$_2$O); 71.8 (OCH$_2$*C*H$_2$O); 81.3 (*C*HOMEM); 95.5 (O*C*H$_2$O); 127.0, 128.2, 128.9 (*C*H$_{arom}$); 139.6 (C_{arom}); 176.3 (*C*O$_2$H). Anal. Calcd for $C_{23}H_{31}NO_5$: C, 68.80; H, 7.78; N, 3.49. Found: C, 69.01; H, 7.95; N, 3.68.

Procedure B ($NaClO_2$/NaH_2PO_4/2-methyl-2-butene). To a solution of aminoaldehyde *syn*-**3** (387 mg, 1 mmol) in 16 mL of *t*-BuOH–CH_3CN (5/3) was added 2-methyl-2-butene (1.3 mL, 12 mmol, 12 equiv.). To this was added a solution containing 80% $NaClO_2$ (678 mg, 6 mmol, 6 equiv.) and $NaH_2PO_4\cdot 2H_2O$ (936 mg, 6 mmol, 6 equiv.) in H_2O (20 mL) dropwise at 0°C. The resulting solution was stirred at 0°C for 30 min and quenched by addition of a 5% $Na_2S_2O_5$ solution (5 mL). The solution was adjusted to pH=6 and the mixture was extracted with ethyl acetate (3×10 mL), the combined organic phases were washed with brine, dried (Na_2SO_4) and the solvent was evaporated. The product was purified by flash chromatography (silica gel, CH_2Cl_2/Et_2O: 5/2) yielding *syn*-**4** as a colorless oil: 261 mg (0.65 mmol, 65%).

(2*R*,3*R*)-2-(*N*,*N*-Dibenzylamino)-3-[(2-methoxyethoxy)-methoxy]-1-pentanoic acid (*anti*-4). The aminoacid *anti*-**4** was obtained from *anti*-**3** (289 mg, 0.75 mmol) by the *procedure A* described for *syn*-**4** and purified by flash chromatography (silica gel, hexane/EtOAc=1/2): 121 mg (0.3 mmol, 40%). The same compound was also prepared from *anti*-**3** (387 mg, 1 mmol) by the *procedure B* described for *syn*-**4** and purified by flash chromatography (CH_2Cl_2/Et_2O: 5/2): 249 mg (0.62 mmol, 62%). Colorless oil. $[\alpha]_D^{23}=+71.7$ (c=1, $CHCl_3$). IR (film): 3500–2500, 1700, 1450, 740, 700 cm^{-1}. ^1H NMR ($CDCl_3$): 0.55 (t, 3H, J=7.4 Hz, CH_3CH$_2$); 1.72 (m, 1H, C*H*HCH$_3$); 1.84 (m, 1H, CH*H*CH$_3$); 3.37 (s, 3H, CH_3O); 3.42 (d, 1H, J=9.9 Hz, C*H*N); 3.47 (d, 2H, J=13.6 Hz, C*H*HPh); 3.54 (m, 2H, OCH_2CH$_2$O); 3.67 (m, 2H, OCH$_2$CH_2O); 3.94 (d, 2H, J=13.6 Hz, CH*H*Ph); 4.12 (m, 1H, C*H*OMEM); 4.70 (d, 1H, J=7.2 Hz, OC*H*HO); 4.73 (d, 1H, J=7.2 Hz, OCH*H*O); 7.20–7.40 (m, 10H, H_{arom}). ^{13}C NMR ($CDCl_3$): 6.7 (*C*H$_3$CH$_2$); 22.4 (*C*H$_2$CH$_3$); 55.1 (*C*H$_2$Ph); 58.9 (*C*H$_3$O); 62.6 (*C*HN); 67.2 (O*C*H$_2$CH$_2$O); 71.7 (OCH$_2$*C*H$_2$O); 76.1 (*C*HOMEM); 95.1 (O*C*H$_2$O); 127.2, 128.2, 129.2 (*C*H$_{arom}$); 138.7 (C_{arom}); 175.8 (*C*O$_2$H). Anal. Calcd for $C_{23}H_{31}NO_5$: C, 68.80; H, 7.78; N, 3.49. Found: C, 68.59; H, 7.82; N, 3.33.

(2*R*,3*S*)-2-(*N*,*N*-Dibenzylamino)-3-hydroxy-1-pentanoic acid (*syn*-5). A mixture of *syn*-**4** (378 mg, 0.94 mmol) and 2N HCl solution in THF-H_2O (13 mL) was stirred overnight at room temperature. The pH of the reaction was adjusted to 6 with saturated $NaHCO_3$ solution and the mixture extracted with ether (3×15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated and chromatographed (CH_2Cl_2/Et_2O: 5/1) to yield *syn*-**5** as a colorless oil: 215 mg (0.67 mmol, 71%). $[\alpha]_D^{23}=+127.4$ (c=2.6, $CHCl_3$). IR (film): 3500–2500, 1700, 1600, 750, 700 cm^{-1}. ^1H NMR ($CDCl_3$): 0.95 (t, 3H, J=7.3 Hz, CH_3CH$_2$); 1.32 (m, 1H, C*H*HCH$_3$); 1.65 (m, 1H, CH*H*CH$_3$); 3.26 (d, 1H, J=9.3 Hz, C*H*N); 3.68 (d, 2H, J=13.2 Hz, C*H*HPh); 3.97 (m, 1H, C*H*OH); 4.10 (d, 2H, J=13.2, CH*H*Ph); 4.21 (br s, 1H, O*H*); 7.20–7.40 (m, 10H, H_{arom}). ^{13}C NMR ($CDCl_3$): 9.8 (*C*H$_3$); 27.1 (*C*H$_2$CH$_3$); 54.8 (*C*H$_2$Ph); 65.8 (*C*HN); 68.3 (*C*HOH); 128.1, 128.7, 129.5 (*C*H$_{arom}$); 135.6 (C_{arom}); 171.8 (*C*O$_2$H). Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.72; H, 7.54; N, 4.62.

(2*R*,3*R*)-2-(*N*,*N*-Dibenzylamino)-3-hydroxy-1-pentanoic acid (*anti*-5). To a 0.1 M solution of *anti*-**4** (100 mg, 0.25 mmol) in dry acetonitrile at −20°C was added NaI (112 mg, 0.75 mmol, 3 equiv.) and TMSCl (0.1 mL, 0.75 mmol, 3 equiv.). The reaction mixture was allowed to rise rt, stirred overnight and quenched with methanol (3 mL) and water (3 mL). The pH of the reaction was adjusted to 6 and the mixture extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with saturated Na_2SO_3 solution and with brine, dried over Na_2SO_4, concentrated and chromatographed (silica gel, hexane/EtOAc: 1/1) to yield *anti*-**5** as a colorless oil: 55 mg (0.17 mmol, 70%). $[\alpha]_D^{23}=+45.5$ (c=0.9, $CHCl_3$). ^1H NMR ($CDCl_3$): 0.83 (t, 3H, J=7.4 Hz, CH_3CH$_2$); 1.35 (m, 1H, C*H*HCH$_3$); 1.86 (m, 1H, CH*H*CH$_3$); 3.21 (d, 1H J=7.5 Hz, C*H*N); 3.74 (d, 2H, J=13.5 Hz, C*H*HPh); 3.85 (m, 3H, CH*H*Ph and C*H*OH); 4.02 (s, 1H, O*H*); 7.20–7.50 (m, 10H, H_{arom}); 7.57 (br s, 1H, CO$_2$*H*). ^{13}C NMR ($CDCl_3$): 9.7 (*C*H$_3$); 27.0 (*C*H$_2$CH$_3$);

55.5 (CH_2Ph); 65.9 (*C*HN); 71.1 (*C*HOH); 127.3, 128.4, 129.2 (CH_{arom}); 138.5 (C_{arom}); 176.0 (CO_2H). Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.63; H, 7.43; N, 4.34.

(2*R*, 3*S*)-3-Hydroxy norvaline (*syn*-6). To a solution of *syn*-**5** (157 mg, 0.5 mmol) in a 1:1 mixture MeOH–H_2O (5 mL) was added 40 mg of 20% $Pd(OH)_2$–C in one portion. The mixture was stirred under hydrogen atmosphere and the reaction was monitored by TLC. After 3 h the reaction was completed, the catalyst was removed by filtration through celite and washed with water. The solvent was concentrated under reduced pressure and the residue was purified by flash chromatography (silica gel, $CH_2Cl_2/CH_3OH/NH_4OH$: 6/4/1), to give *syn*-**6** as a colorless solid: 56 mg (0.43 mmol, 85%). Mp 229–230°C (dec) (H_2O/acetone). $[\alpha]_D^{23}=+7.9$ (c=0.82, H_2O). [Lit.[20b]: mp 232–233°C; $[\alpha]_D^{23}=+7.8$ (c=0.85, H_2O)]. ^{1}H NMR (D_2O): 0.87 (t, 3H, J=7.4 Hz, CH_3); 1.49 (m, 2H, CH_2); 3.58 (d, 1H, J=4.2 Hz, C*H*N); 3.88 (m, 1H, C*H*OH). ^{13}C NMR (D_2O): 11.8 (CH_3); 28.8 (CH_2); 61.1 (*C*HN); 73.7 (*C*HOH); 175.6 (CO_2H).

(2*R*, 3*R*)-3-Hydroxy norvaline (*anti*-6). The aminoacid *anti*-**6** was obtained by debenzylation of *anti*-**5** (47 mg, 0.15 mmol) and purified as described for *syn*-**6**: 18 mg (0.13 mmol, 90%). Colorless solid, mp 223–224°C (dec) (H_2O/acetone). $[\alpha]_D^{23}=-4.6$ (c=0.9, H_2O). $[\alpha]_D^{23}=-25.4$ (c=1, 1N HCl). [Lit.[9c]: mp 222–224°C; $[\alpha]_D^{23}=-24.3$ (c=1, 1N HCl; Lit.[20a]: $[\alpha]_D^{23}=-0.3$ (c=1, 1N HCl)]. ^{1}H NMR (D_2O): 0.80 (t, 3H, J=7.4 Hz, CH_3); 1.34 (m, 2H, CH_2); 3.65 (d, 1H, J=3.7 Hz, C*H*N); 3.82 (m, 1H, C*H*OH). ^{13}C NMR (D_2O): 12.4 (CH_3); 26.7 (CH_2); 61.7 (*C*HN); 73.8 (*C*HOH); 174.5 (CO_2H).

***N*-Benzyl, *N*-benzoyl-2-amino-2-penten-1-al (7).** A solution of aminoaldehyde *syn*-**3** (289 mg, 0.75 mmol) in a acetonitrile (3 mL)-CCl_4 (3 mL)-water (4 mL)-acetone (1 mL) was stirred with solid $NaIO_4$ (642 mg, 3 mmol) at room temperature. After 15 min, hydrated RuO_2 (3 mg) was added and the mixture was stirred for a further 1 h. The mixture was treated with propan-2-ol (1 mL) and filtered through a Celite pad. The solvent was removed and the residue was chromatographed over silica gel (hexane/EtOAc: 8/1) to give 7 as a colorless solid: 26 mg (0.09 mmol, 12%). Mp 107–108°C (from hexane). ^{1}H NMR ($CDCl_3$): 0.41 (t, 3H, J=7.5 Hz, CH_3); 1.60 (m, 2H, CH_2CH$_3$); 4.16 (d, 1H, J=14.1 Hz, C*H*HPh); 5.55 (d, 1H, J=14.1 Hz, CH*H*Ph); 6.22 (dd, 1H, J=8.4 Hz, J=6.6 Hz, C*H*=C); 7.20–7.40 (m, 10H, H_{arom}); 9.25 (s, 1H, C*H*O). ^{13}C NMR ($CDCl_3$): 11.3 (CH_3); 22.2 (CH_2); 49.8 (CH_2Ph); 127.2, 127.8, 128.3, 129.8, 130.2 (CH_{arom}); 135.8, 136.5 (C_{arom}); 141.2 (*C*=CH); 157.1 (*C*H=C); 170.9 (*C*ON); 190.1 (*C*HO). Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.68; H, 6.65; N, 4.82.

(*S*)-*N*,*N*-Dibenzyl-2-[(2-methoxyethoxy)methoxy]-butyramide (8). The compound **8** was obtained as the minor product in the oxidation of the aminoaldehyde *syn*-**3** by the procedure B: 104 mg (0.28 mmol, 28%). Colorless oil. $[\alpha]_D^{23}=-44.1$ (c=1, $CHCl_3$). IR (film): 2910, 1640, 730, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$): 0.96 (t, 3H, J=7.4 Hz, CH_3CH$_2$); 1.82 (m, 2H, CH_2CH$_3$); 3.33 (s, 3H, CH_3O); 3.46 (m, 2H, OCH_2CH$_2$O); 3.71 (m, 2H, OCH$_2$CH_2O); 4.44 (dd, 1H, J=7.8 Hz, J=4.8 Hz, C*H*OMEM); 4.49 (d, 1H, J=14.6 Hz, C*H*HPh); 4.52 (s, 2H, CH_2Ph); 4.69 (d, 1H, J=14.6 Hz, CH*H*Ph); 7.20–7.40 (m, 10H, H_{arom}). ^{13}C NMR ($CDCl_3$): 10.1 (CH_3CH_2); 26.1 (CH_2CH_3); 48.0 (CH_2Ph); 49.1 (CH_2Ph); 58.9 (CH_3O); 67.2 (OCH_2CH_2O); 71.5 (OCH_2CH_2O); 75.4 (*C*HOMEM); 94.5 (OCH_2O); 126.7, 127.4, 127.6, 128.4, 128.5, 128.8 (CH_{arom}); 136.4, 137.0 (C_{arom}); 172.3 (*C*=O). Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77. Found: C, 70.96; H, 7.96; N, 3.83.

(*R*)-*N*,*N*-Dibenzyl-2-[(2-methoxyethoxy)methoxy]-butyramide (*ent*-8). This compound was obtained as the minor product in the oxidation of the aminoaldehyde *anti*-**3** by the *procedure B*: 104 mg (0.22 mmol, 22%). Colorless oil. $[\alpha]_D^{23}=+41.8$ (c=0.7, $CHCl_3$). Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77. Found: C, 71.01; H, 7.77; N, 3.80.

(2*S*, 3*S*)-2-Amino-3-[(2-methoxyethoxy)methoxy]-1-pentanol (*syn*-9). To a solution of *syn*-**2** (1.72 g, 4.4 mmol) in methanol (50 mL) was added $Pd(OH)_2$–C (340 mg) in one portion. The mixture was stirred under hydrogen for 3.5 h and the catalyst was removed by filtration through celite and washed with methanol. The solvent was evaporated under reduced pressure to afford the pure product *syn*-**9** as a colorless oil: 0.92 g (4.4 mmol, 100%). $[\alpha]_D^{23}=+51.3$ (c=1.2, $CHCl_3$). IR (film): 3340, 1450, 1030 cm^{-1}. ^{1}H NMR ($CDCl_3$): 0.92 (t, 3H, J=7.4 Hz, CH_3CH$_2$); 1.62 (m, 2H, CH_2CH$_3$); 2.96 (m, 1H, C*H*NH$_2$); 3.25 (br s, 3H, O*H* and NH_2); 3.40 (s, 3H, CH_3O); 3.55 (m, 4H); 3.67 (m, 2H); 3.80 (m, 1H); 4.74 (d, 1H, J=7.0 Hz, OC*H*HO); 4.79 (d, 1H, J=7.0 Hz, OCH*H*O). ^{13}C NMR ($CDCl_3$): 9.4 (CH_3CH_2); 23.5 (CH_2CH_3); 54.3 ($CHNH_2$); 59.0 (CH_3O); 63.1 (CH_2OH); 67.4 (OCH_2CH_2O); 71.6 (OCH_2CH_2O); 79.2 (*C*HOMEM); 95.0 (OCH_2O). Anal. Calcd for $C_9H_{21}NO_4$: C, 52.15; H, 10.21; N, 6.76. Found: C, 51.92; H, 10.10; N, 6.70.

(2*S*, 3*R*)-2-Amino-3-[(2-methoxyethoxy)methoxy]-1-pentanol (*anti*-9). The debenzylated aminoalcohol *anti*-**9** was obtained from *anti*-**2** (2.0 g, 5.2 mmol) by the procedure described for *syn*-**9**: 992 mg (4.79 mmol, 92%). Colorless oil. $[\alpha]_D^{23}=-56.1$ (c=1, $CHCl_3$). IR (film): 3300, 1585, 1025 cm^{-1}. ^{1}H NMR ($CDCl_3$): 0.87 (t, 3H, J=7.4 Hz, CH_3CH$_2$); 1.52 (m, 2H, CH_2CH$_3$); 2.98 (m, 1H, C*H*NH$_2$); 3.26 (br s, 3H, O*H* and NH_2); 3.32 (s, 3H, CH_3O); 3.51 (m, 3H, OCH_2CH$_2$O and C*H*OMEM); 3.60 (m, 3H, OCH$_2$C*H*HO and CH_2OH); 3.69 (m, 1H, OCH$_2$CH*H*O); 4.67 (d, 1H, J=7.1 Hz, OC*H*HO); 4.71 (d, 1H, J=7.1 Hz, OCH*H*O). ^{13}C NMR ($CDCl_3$): 9.5 (CH_3CH_2); 23.5 (CH_2CH_3); 54.4 ($CHNH_2$); 58.8 (CH_3O); 61.9 (CH_2OH); 67.3 (OCH_2CH_2O); 71.5 (OCH_2CH_2O); 81.2 (*C*HOMEM); 95.3 (OCH_2O). Anal. Calcd for $C_9H_{21}NO_4$: C, 52.15; H, 10.21; N, 6.76. Found: C, 51.99; H, 10.39; N, 6.83.

(2*S*,3*S*)-2-[*tert*-Butoxycarbonylamino]-3-[(2-methoxyethoxy)-methoxy]-1-pentanol (*syn*-10). A solution of *syn*-**9** (483 mg, 2.33 mmol) and di-*tert*-butyl dicarbonate (537 mg, 2.46 mmol, 1.05 equiv.) in anhydrous CH_2Cl_2 (15 mL) under argon was kept at 20°C for 5 h. At this time, the reaction was quenched with water (30 mL) and the aqueous layer was extracted with two 25 mL portions

of CH_2Cl_2. The combined organic extracts were washed with a saturated $NaHCO_3$ solution and worked up as usual. The crude product was purified by flash chromatography (silica gel, hexane/EtOAc: 2/3) to yield *syn*-**10** as a colorless oil: 702 mg (2.28 mmol, 98%). $[\alpha]_D^{23}=+53.2$ (c=1, $CHCl_3$). IR (film): 3440, 1700, 1495, 1040, 840 cm^{-1}. ^1H NMR ($CDCl_3$): 0.87 (t, 3H, J=7.5 Hz, CH_3CH$_2$); 1.38 (s, 9H, (CH_3)$_3$C); 1.54 (m, 2H, CH_2CH$_3$); 3.34 (s, 3H, CH_3O); 3.57 (m, 5H, CH_2OH, OCH_2CH$_2$O and CHN); 3.74 (m, 3H, CHOMEM and OCH$_2$CH_2O); 4.65 (d, 1H, J=6.9 Hz, OCHHO); 4.72 (d, 1H, J=6.9 Hz, OCHHO); 4.88 (d, 1H, J=9.2 Hz, NH). ^{13}C NMR ($CDCl_3$): 9.7 (*C*H$_3$CH$_2$); 23.7 (*C*H$_2$CH$_3$); 28.2 (*C*H$_3$)$_3$C); 53.0 (*C*HN); 58.9 (*C*H$_3$O); 62.4 (*C*H$_2$OH); 67.2 (O*C*H$_2$CH$_2$O); 71.5 (OCH$_2$*C*H$_2$O); 76.9 (*C*HOMEM); 79.2 (*C*(CH$_3$)$_3$); 94.3 (OCH$_2$O); 156.1 (*C*=O). Anal. Calcd for $C_{14}H_{29}NO_6$: C, 54.70; H, 9.51; N, 4.56. Found: C, 54.56; H, 9.32; N, 4.44.

(2*S*,3*R*)-2-[*tert*-Butoxycarbonylamino]-3-[(2-methoxyethoxy)-methoxy]-1-pentanol (*anti*-10). The compound *anti*-**10** was obtained from *anti*-**9** (932 mg, 4.5 mmol) by the method described for *syn*-**10**: 1.25 g (4.05 mmol, 90%). Colorless oil. IR (film): 3420, 3320, 1690 cm^{-1}. $[\alpha]_D^{23}=-40.4$ (c=1.2, $CHCl_3$). ^1H NMR ($CDCl_3$): 0.95 t, 3H, J=7.4 Hz, CH_3CH$_2$); 1.45 (s, 9H, (CH_3)$_3$C); 1.62 (m, 2H, CH_2CH$_3$); 3.12 (m, 1H, CHN); 3.40 (s, 3H, CH_3O); 3.58 (m, 2H, OCH_2CH$_2$O); 3.65 (m, 4H, OCHHCH$_2$O and CH$_2$OH); 3.82 (m, 1H, OCHHCH$_2$O); 4.73 (d, 1H, J=7.1 Hz, OCHHO); 4.76 (d, 1H, J=7.1 Hz, OCHHO); 5.53 (d, 1H, J=7.1 Hz, NH). C NMR ($CDCl_3$): 9.5 (*C*H$_3$CH$_2$); 24.5 (*C*H$_2$CH$_3$); 28.3 (*C*H$_3$)$_3$C); 53.4 (*C*HN); 58.9 (*C*H$_3$O); 61.8 (*C*H$_2$OH); 67.5 (O*C*H$_2$CH$_2$O); 71.5 (OCH$_2$*C*H$_2$O); 79.2 (*C*(CH$_3$)$_3$); 81.3 (*C*HOMEM); 95.6 (OCH$_2$O); 156.0 (*C*=O). Anal. Calcd for $C_{14}H_{29}NO_6$: C, 54.70; H, 9.51; N, 4.56. Found: C, 54.58; H, 9.42; N, 4.48.

(2*R*,3*S*)-2-[*tert*-Butoxycarbonylamino]-3-[(2-methoxyethoxy)-methoxy]-1-pentanoic acid (*syn*-11). To a solution of *syn*-**10** (461 mg, 1.5 mmol) in freshly distilled dimethylformamide (6 mL) was slowly added PDC (2.82 g, 7.5 mmol, 5 equiv.). The orange suspension was stirred at room temperature overnight, and quenched by addition of H_2O (40 mL). The solution was extracted with ether (6×20 mL), the combined ethereal layers were washed with H_2O and saturated NaCl solution, dried (Na_2SO_4) and the volatiles were evaporated. The residue was purified by flash chromatography (silica gel, EtOAc/EtOH: 2/1) to yield *syn*-**11** as a colorless oil: 289 mg (0.9 mmol, 60%). $[\alpha]_D^{23}=-26.7$ (c=1, MeOH). IR (film): 3300, 1710, 1035 cm^{-1}. ^1H NMR ($CDCl_3$): 0.95 (t, 3H, J=7.4 Hz, CH_3CH$_2$); 1.44 (s, 9H, (CH_3)$_3$C); 1.62 (m, 2H, CH_2CH$_3$); 3.38 (s, 3H, CH_3O); 3.54 (m, 3H, OCHHCH_2O); 3.72 (m, 1H, OCHHCH$_2$O); 4.09 (m, 1H, CHOMEM); 4.44 (d, 1H, J=9.7 Hz, CHN); 4.68 (d, 1H, J=7.1 Hz, OCHHO); 4.74 (d, 1H, J=7.1 Hz, OCHHO); 5.33 (d, 1H, NH); 9.20 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$): 10.1 (*C*H$_3$CH$_2$); 24.6 (*C*H$_2$CH$_3$); 28.3 ((*C*H$_3$)$_3$C); 56.9 (*C*HN); 58.9 (*C*H$_3$O); 67.2 (O*C*H$_2$CH$_2$O); 71.6 (OCH$_2$*C*H$_2$O); 79.4 (*C*HOMEM); 80.3 (*C*(CH$_3$)$_3$); 95.2 (OCH$_2$O); 156.2 (N*C*O$_2$*t*Bu); 177.4 (*C*O$_2$H). Anal. Calcd for $C_{14}H_{27}NO_7$: C, 52.32; H, 8.47; N, 4.36. Found: C, 52.27; H, 8.32; N, 4.40.

(2*R*,3*R*)-2-[*tert*-Butoxycarbonylamino]-3-[(2-methoxyethoxy)methoxy]-1-pentanoic acid (*anti*-11). The protected aminoacid *anti*-**11** was prepared from *anti*-**10** (922 mg, 3.0 mmol) as described for *syn*-**11**: 713 mg (2.22 mmol, 74% yield). Colorless oil. $[\alpha]_D^{23}=-25.1$ (c=0.94, $CHCl_3$). IR (film): 3340, 1710, 1040 cm^{-1}. ^1H NMR ($CDCl_3$): 0.98 (t, 3H, J=7.4 Hz, CH_3CH$_2$); 1.45 (s, 9H, (CH_3)$_3$C); 1.73 (m, 2H, CH_2CH$_3$); 3.42 (m, 3H, CH_3O); 3.55–3.78 (m, 4H, OCHHCH_2O and CHOMEM); 3.86 (m, 1H, OCHHCH$_2$O); 4.45 (d, 1H, J=7.2 Hz, CHN); 4.73 (d, 1H, J=7.4 Hz, OCHHO); 4.81 (d, 1H, J=7.4 Hz, OCHHO); 5.92 (d, 1H, J=8.4 Hz, NH); 8.70 (br s, 1H, CO$_2$$H$). ^{13}C NMR ($CDCl_3$): 10.1 (*C*H$_3CH_2$); 24.9 (*C*H$_2CH_3$); 28.2 (C(*C*H$_3$)$_3$); 56.0 (*C*HN); 58.8 (*C*H$_3$O); 67.4 (*C*H$_2$O); 71.4 (*C*H$_2$O); 79.7 (*C*(CH$_3$)$_3$); 82.0 (*C*HOMEM); 95.6 (OCH$_2$O); 155.5 (N*C*O$_2$*t*Bu); 173.7 (*C*O$_2$H). Anal. Calcd for $C_{14}H_{27}NO_7$: C, 52.32; H, 8.47; N, 4.36. Found: C, 52.12; H, 8.24; N, 4.28.

Experimental procedure for deprotection of amino acids 11

2N HCl solution in THF-H_2O (1:1) was added to *syn*-**11** (244 mg, 0.76 mmol) and the solution was stirred at rt overnight. The THF was eliminated on Rotavapor, the mixture was extracted with ether (2×10 mL) and the aqueous layer was evaporated in vacuo. Anhydrous ethanol (10 mL) and a large excess of propylene oxide (4 mL) was added to the solid residue and the mixture was refluxed for 30 min. After removal of the volatiles on Rotavapor, the white residue was purified by flash chromatography (silica gel, CH_2Cl_2/CH_3OH/NH_4OH: 6/4/1), to give *syn*-**6** as a colorless solid: 61 mg (0.46 mmol, 60%). The compound *anti*-**11** (406 mg, 1.26 mmol) was deprotected by the same procedure to afford *anti*-**6** as a colorless solid: 105 mg (0.79 mmol, 62%).

1-[(1*S*)-1-Amino-2-hydroxyethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2.]octane (13). Compound **12** (4.53 g, 14 mmol) was debenzylated as described for *syn*-**9** to yield **13** as a colorless solid: 2.62 g (13.8 mmol, 99%). Mp 101–103°C (from hexane). $[\alpha]_D^{23}=-12.8$ (c=0.5, $CHCl_3$). IR (KBr): 3400 cm^{-1}. ^1H NMR ($CDCl_3$): 0.82 (s, 3H, CH_3); 3.17 (dd, 1H, J=7.6 Hz, J=4.1 Hz, CHN); 3.69 (dd, 1H, J=11.7 Hz, J=7.6 Hz, CHHOH); 3.83 (dd, 1H, J=11.7 Hz, J=4.1 Hz, CHHOH); 3.94 (m, 6H, CH_2); 4.88 (br s, 3H, NH_2 and OH). ^{13}C NMR ($CDCl_3$): 14.1 (*C*H$_3$); 30.4 (*C*(CH$_3$)); 56.1 (*C*HN); 60.0 (*C*H$_2$OH); 72.5 (*C*H$_2$O); 107.3 (*C*O$_3$). Anal. Calcd for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40. Found: C, 50.93; H, 7.78; N, 7.21.

1-[*N*,*N*-Dibenzyl-(1*S*)-1-amino-2-hydroxyethyl]-4-methyl-2,6,7-trioxabicyclo [2.2.2.]octane (14). A mixture of **13** (2.62 g, 13.8 mmol), benzyl bromide (3.61 mL, 30.4 mmol, 2.2 equiv.) and K_2CO_3 (4.57 g, 33.1 mmol, 2.4 equiv.) in acetonitrile (85 mL) was stirred at room temperature overnight. The solid was separated by filtration, the filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (silica gel, hexane/EtOAc: 6/1) to yield **14** as a colorless solid: 4.13 g (11.2 mmol, 81%). Mp 82–83°C (from hexane). $[\alpha]_D^{23}=-113$ (c=1.1, $CHCl_3$). IR (KBr): 3420, 1610, 1450, 745, 700 cm^{-1}. ^1H NMR ($CDCl_3$): 0.78 (s, 3H, CH_3); 2.70 (br s, 1H, OH); 2.98 (dd, 1H, J=9.1 Hz,

J=5.5 Hz, C*H*N); 3.57 (dd, 1H, J=10.5 Hz, J=5.5 Hz, C*H*HOH); 3.62 (dd, 1H, J=10.5 Hz, J=9.1 Hz, CH*H*OH); 3.83 (d, 2H, J=13.5 Hz, C*H*HPh); 3.88 (m, 6H, CH_2); 3.98 (d, 2H, J=13.5 Hz, CH*H*Ph); 7.15–7.35 (m, 10H, H_{arom}). ^{13}C NMR ($CDCl_3$): 14.5 (CH_3); 30.2 ($C(CH_3)$); 54.3 (CH_2Ph); 58.1 (CH_2OH); 61.7 (*C*HN); 71.9 (CH_2O); 109.7 (CO_3); 126.8, 128.2; 129.2 (CH_{arom}); 140.2 (C_{arom}). Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.32; H, 7.20; N, 3.68.

1-[*N*,*N*-Dibenzyl-(1*S*)-1-amino-2-oxoethyl]-4-methyl-2,6,7-trioxabicyclo [2.2.2.]octane (15). To a stirred solution of oxalyl chloride (0.65 mL, 7.45 mmol) in dichloromethane (15 mL) at −78°C under argon was added dimethyl sulfoxide (1.1 mL, 15.5 mmol). After 15 min, a solution of aminoalcohol **14** (2.03 g, 5.5 mmol) in dichloromethane (15 mL) was added, and the mixture was stirred for 30 min at −78°C before addition of triethylamine (2.2 mL, 15.8 mmol). Then, the reaction was allowed to reach the room temperature under stirring for 45 min and the mixture quenched with water (15 mL). The aqueous phase was extracted with dichloromethane (15 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$) and concentrated to yield an oil that was used without further purification in the next step: 2.00 g (5.4 mmol, 99%). Colorless solid, mp 106–108°C (from hexane). $[\alpha]_D^{23}$=−106.8 (c=0.9, $CHCl_3$). IR (KBr): 1715, 1585, 740, 690 cm^{-1}. ^{1}H NMR ($CDCl_3$): 0.83 (s, 3H, CH_3); 3.46 (s, 1H, C*H*N); 3.95 (m, 10H, CH_2O and CH_2Ph); 7.18–7.45 (m, 10H, H_{arom}); 9.75 (s, 1H, C*H*O). ^{13}C NMR ($CDCl_3$): 14.5 (CH_3); 30.7 (CCH_3); 55.1 (CH_2Ph); 69.5 (*C*HN); 72.3 (CH_2O); 109.2 (CO_3); 126.7, 128.1, 128.9 (CH_{arom}); 140.3 (C_{arom}); 200.2 (*C*HO). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.76; H, 6.70; N, 3.58.

Alkylation of aminoaldehyde 15 with R_2Zn

General method. To a solution of aminoaldehyde **15.** (368 mg, 1 mmol) in anhydrous toluene (10 mL) at 0°C (ice bath) under argon was added dropwise a 1 M solution of dialkylzinc in hexane or toluene (4 mmol, 4 equiv.). The mixture was stirred at that temperature until the reaction was finished (TLC), and then quenched with aqueous saturated solution of ammonium chloride (30 mL). The organic layer was separated and the aqueous phase was extracted with diethyl ether (2×20 mL). The combined organic layers were washed with brine, and dried over anhydrous Na_2SO_4. The solvents were eliminated under vacuum and the residue was purified by flash chromatography.

1-[*N*,*N*-Dibenzyl-(1*S*,2*R*)-1-amino-2-hydroxypropyl]-4-methyl-2,6,7-trioxabicyclo [2.2.2.]octane (*syn*-16a). Compound *syn*-**16a** was obtained from **15** (276 mg, 0.75 mmol) by reaction with Me_2Zn. The product was purified by flash chromatography (silica gel, hexane/Et_2O: 4/1): 78 mg (0.20 mmol, 27%). Colorless solid, mp 82–83°C (from hexane). $[\alpha]_D^{23}$=−88.6 (c=0.4, $CHCl_3$). IR (KBr): 3300, 1430, 730, 690 cm^{-1} ^{1}H NMR ($CDCl_3$): 0.83 (s, 3H, CH_3); 1.10 (d, 3H, J=6.0 Hz, CH_3CH); 2.54 (d, 1H, J=8.4 Hz, C*H*N); 3.83 (d, 2H, J=13.4 Hz, C*H*HPh); 3.89 (m, 2H, C*H*OH and O*H*); 3.92 (s, 6H, CH_2O); 4.03 (d, 2H, J=13.4 Hz, CH*H*Ph); 7.15–7.35 (m, 10H, H_{arom}). ^{13}C NMR ($CDCl_3$): 14.6 (CH_3); 19.7 (CH_3CH); 30.4 (CCH_3); 55.1 (CH_2Ph); 63.8 (*C*HN); 66.8 (*C*HOH); 71.8 (CH_2O); 110.0 (CO_3); 126.9, 128.3, 129.5 (CH_{arom}); 140.0 (C_{arom}). Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 71.88; H, 7.73; N, 3.77.

1-[*N*,*N*-Dibenzyl-(1*S*,2*R*)-1-amino-2-hydroxybutyl]-4-methyl-2,6,7-trioxabicyclo [2.2.2.]octane (*syn*-16b). Compound *syn*-**16b** was obtained from **15** (368 mg, 1 mmol) by reaction with Et_2Zn. The product was purified by flash chromatography (silica gel, hexane/EtOAc: 8/1): 246 mg (0.62 mmol, 62%). $[\alpha]_D^{23}$=−71.5 (c=1, $CHCl_3$). Colorless solid, mp 78–80°C (from hexane). IR (KBr): 3400, 1460, 745, 690 cm^{-1}. ^{1}H NMR ($CDCl_3$): 0.80 (t, 3H, J=7.4 Hz, CH_3CH$_2$); 0.84 (s, 3H, CH_3); 1.24 (m, 1H, C*H*HCH$_3$); 1.65 (m, 1H, CH*H*CH$_3$); 2.63 (d, 1H, J=8.0 Hz, C*H*N); 3.71 (dt, 1H, J=8.0 Hz, J=3.1 Hz, C*H*OH); 3.83 (d, 2H, J=13.4 Hz, C*H*HPh); 3.92 (m, 6H, CH_2O); 4.03 (d, 2H, J=13.4 Hz, CH*H*Ph); 7.15–7.30 (m, 10H, H_{arom}). ^{13}C NMR ($CDCl_3$): 10.1 (CH_3CH_2); 14.6 (CH_3); 26.4 (CH_2CH_3); 30.4 (CCH_3); 55.1 (CH_2Ph); 64.5 (*C*HN); 68.7 (*C*HOH); 71.8 (CH_2O); 110.2 (CO_3); 126.8, 128.2, 129.5 (CH_{arom}); 140.0 (C_{arom}). Anal. Calcd for $C_{24}H_{31}NO_4$: C, 72.52; H, 7.86; N, 3.52. Found: C, 72.29; H, 7.82; N, 3.73.

1-[*N*,*N*-Dibenzyl-(1*S*,2*R*)-1-amino-2-hydroxy-3-methylbutyl]-4-methyl-2,6,7-trioxabicyclo [2.2.2.]octane (*syn*-16c). Compound *syn*-**16c** was obtained from **15** (368 mg, 1 mmol) by reaction with *i*-Pr_2Zn. The product was purified by flash chromatography (silica gel, hexane/EtOAc: 8/1): 324 mg (0.79 mmol, 79%). Colorless solid, mp 92–93°C (from hexane). $[\alpha]_D^{23}$=−77.8 (c=1.2, $CHCl_3$). IR (KBr): 3400, 1435, 740, 690 cm^{-1}. ^{1}H NMR ($CDCl_3$): 0.46 (d, 3H, J=6.6 Hz, CH_3CH); 0.81 (s, 3H, CH_3); 0.89 (d, 3H, J=7.0 Hz, CH_3CH); 1.91 (m, 1H, CH(CH$_3$)$_2$); 2.81 (d, 1H, J=8.8 Hz, C*H*N); 3.68 (dd, 1H, J=8.8 Hz, J=2.5 Hz, C*H*OH); 3.83 (d, 2H, J=13.2 Hz, C*H*HPh); 3.89 (s, 6H, CH_2O); 4.02 (d, 2H, J=13.2 Hz, CH*H*Ph); 7.15–7.30 (m, 10H, H_{arom}). ^{13}C NMR ($CDCl_3$): 14.0 (CH_3CH); 14.6 (CH_3); 21.3 (CH_3CH); 28.8 ($CH(CH_3)_2$); 30.3 (CCH_3); 54.9 (CH_2Ph); 61.8 (*C*HN); 70.4 (*C*HOH); 71.7 (CH_2O); 110.3 (CO_3); 126.8, 128.2, 129.6 (CH_{arom}); 139.9 (C_{arom}). Anal. Calcd for $C_{25}H_{33}NO_4$: C, 72.96; H, 8.08; N, 3.40. Found: C, 72.84; H, 8.21; N, 3.54.

1-[*N*,*N*-Dibenzyl-(1*S*,2*R*)-1-amino-2-hydroxy-2-phenylethyl]-4-methyl-2,6,7-trioxabicyclo [2.2.2.]octane (*syn*-16d). Compound *syn*-**16d** was obtained as the major diastereomer in the reaction of **15** (300 mg, 0.82 mmol) with Ph_2Zn and purified by flash chromatography (silica gel, hexane/EtOAc: 6/1): 171 mg (0.38 mmol, 47%). Colorless oil. $[\alpha]_D^{23}$=−71.8 (c=0.4, $CHCl_3$). IR (film): 3360, 1600, 745, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$): 0.75 (s, 3H, CH_3); 2.93 (d, 1H, J=8.7 Hz, C*H*N); 3.73 (m, 6H, CH_2O); 3.88 (d, 2H, J=13.3 Hz, C*H*HPh); 4.12 (d, 2H, J=13.3 Hz, CH*H*Ph); 4.68 (br s, 1H, O*H*); 4.82 (d, 1H, J=8.7 Hz, C*H*OH); 7.05–7.40 (m, 15H, H_{arom}). ^{13}C NMR ($CDCl_3$): 14.5 (CH_3); 30.4 (CCH_3); 54.8 (CH_2Ph); 66.8 (*C*HN); 69.6 (*C*HOH); 71.5 (CH_2O); 109.8 (CO_3); 126.7, 127.0, 127.3, 127.4, 128.4, 129.5 (CH_{arom}); 139.6, 143.1 (C_{arom}). Anal.

Calcd for $C_{28}H_{31}NO_4$: C, 75.48; H, 7.01; N, 3.14. Found: C, 75.29; H, 7.09; N, 3.26.

Alkylation of aminoaldehyde 15 with RMgX.

General method. To a solution of aminoaldehyde **15** (368 mg, 1 mmol) in ether (10 mL) at 0°C was added 1 M solution of RMgX in ether (2 mL, 2 mmol, 2 equiv.). After stirring at this temperature until the reaction was finished (TLC), saturated NH_4Cl solution (10 mL) was added and the mixture was extracted with ether (3×10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent evaporated under vacuum. The residue was purified by flash chromatography.

1-[*N*,*N*-Dibenzyl-(1*S*,2*S*)-1-amino-2-hydroxypropyl]-4-methyl-2,6,7-trioxabicyclo [2.2.2.]octane (*anti*-16a). Compound *anti*-**16a** was obtained as the major diastereomer in the reaction of **15** (276 mg, 0.75 mmol) with MeMgI and purified by flash chromatography (silica gel, hexane/Et_2O: 4/1): 115 mg (0.3 mmol, 40%). Colorless solid, mp 107–109°C (from hexane). $[\alpha]_D^{23}=-106.9$ (c=1.6, $CHCl_3$). IR (KBr): 3480, 1445, 745, 690 cm^{-1}. ^1H NMR ($CDCl_3$): 0.85 (s, 3H, C*H*$_3$); 1.14 (d, 3H, J=6.2 Hz, C*H*$_3$CH); 2.66 (d, 1H, J=8.7 Hz, C*H*N); 3.37 (br s, 1H, O*H*); 3.83 (d, 2H, J=13.7 Hz, C*H*HPh); 3.92 (d, 2H, J=13.7 Hz, CH*H*Ph); 3.97 (s, 6H, C*H*$_2$O); 4.08 (m, 1H, C*H*OH); 7.15–7.35 (m, 10H, H_{arom}). ^{13}C NMR ($CDCl_3$): 14.4 (*C*H$_3$); 21.1 (*C*H$_3$CH); 30.2 (*C*CH$_3$); 55.4 (*C*H$_2$Ph); 64.8 (*C*HN); 66.4 (*C*HOH); 71.7 (*C*H$_2$O); 110.9 (*C*O$_3$); 126.5, 127.9, 129.2 (*C*H$_{arom}$); 140.4 (C_{arom}). Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 71.84; H, 7.69; N, 3.55.

1-[*N*,*N*-Dibenzyl-(1*S*,2*S*)-1-amino-2-hydroxybutyl]-4-methyl-2,6,7-trioxabicyclo [2.2.2.]octane (*anti*-16b). Compound *anti*-**16b** was obtained as the major diastereomer in the reaction of **15** (368 mg, 1 mmol) with EtMgBr and purified by flash chromatography (silica gel, hexane/EtOAc: 8/1): 166 mg (0.42 mmol, 42%). $[\alpha]_D^{23}=-93.3$ (c=1.3, $CHCl_3$). Colorless solid, mp 96–98°C (from hexane). IR (KBr): 3480, 1450, 750, 700 cm^{-1}. ^1H NMR ($CDCl_3$): 0.75 (t, 3H, J=7.4 Hz, C*H*$_3$CH$_2$); 0.85 (s, 3H, C*H*$_3$); 1.18 (m, 1H, C*H*HCH$_3$); 1.88 (m, 1H, CH*H*CH$_3$); 2.74 (d, 1H, J=8.8 Hz, C*H*N); 3.33 (br s, 1H, O*H*); 3.80 (m, 1H, C*H*OH); 3.83 (d, 2H, J=13.7 Hz, C*H*HPh); 3.92 (d, 2H, J=13.7 Hz, CH*H*Ph); 3.97 (m, 6H, C*H*$_2$O); 7.15–7.35 (m, 10H, H_{arom}). ^{13}C NMR ($CDCl_3$): 9.6 (*C*H$_3$CH$_2$); 14.6 (*C*H$_3$); 26.9 (*C*H$_2$CH$_3$); 30.4 (*C*CH$_3$); 55.5 (*C*H$_2$Ph); 63.1 (*C*HN); 71.3 (*C*HOH); 71.8 (*C*H$_2$O); 111.1 (*C*O$_3$); 126.6, 128.0, 129.4 (*C*H$_{arom}$); 140.5 (C_{arom}). Anal. Calcd for $C_{24}H_{31}NO_4$: C, 72.52; H, 7.86; N, 3.52. Found: C, 72.65; H, 7.83; N, 3.45.

1-[*N*,*N*-Dibenzyl-(1*S*,2*S*)-1-amino-2-hydroxy-3-methylbutyl]-4-methyl-2,6,7-trioxabicyclo [2.2.2.]octane (*anti*-16c). The compound was obtained as the major diastereomer in the reaction of **15** (294 mg, 0.8 mmol) with *i*-PrMgCl and purified by flash chromatography (silica gel, hexane/EtOAc: 6/1): 127 mg (0.31 mmol, 39%). Colorless solid, mp 149–150°C (from hexane). $[\alpha]_D^{23}=-89.5$ (c=0.9, $CHCl_3$). IR (KBr): 3470, 1440, 740, 690 cm^{-1}. ^1H NMR ($CDCl_3$): 0.16 (d, 3H, J=6.7 Hz, C*H*$_3$CH); 0.84 (s, 3H, C*H*$_3$); 0.92 (d, 3H, J=7.1 Hz, C*H*$_3$CH); 2.15 (m, 1H, C*H*(CH$_3$)$_2$); 2.81 (d, 1H, J=9.6 Hz, C*H*N); 3.16 (br s, 1H, O*H*); 3.70 (dd, 1H, J=9.6 Hz, J=2.0 Hz, C*H*OH); 3.81 (d, 2H, J=13.5 Hz, C*H*HPh); 3.92 (d, 2H, J=13.5 Hz, CH*H*Ph); 3.97 (s, 6H, C*H*$_2$O); 7.15–7.35 (m, 10H, H_{arom}). ^{13}C NMR ($CDCl_3$): 13.4 (*C*H$_3$); 14.5 (*C*H$_3$CH); 20.8 (*C*H$_3$CH); 28.4 (*C*H(CH$_3$)$_2$); 30.4 (*C*CH$_3$); 55.4 (*C*H$_2$Ph); 60.8 (*C*HN); 71.8 (*C*H$_2$O); 73.8 (*C*HOH); 111.2 (*C*O$_3$); 126.6, 128.0, 129.6 (*C*H$_{arom}$); 140.5 (C_{arom}). Anal. Calcd for $C_{25}H_{33}NO_4$: C, 72.96; H, 8.08; N, 3.40. Found: C, 72.71; H, 8.04; N, 3.35.

1-[*N*,*N*-Dibenzyl-(1*S*,2*S*)-1-amino-2-hydroxy-2-phenylethyl]-4-methyl-2,6,7-trioxabicyclo [2.2.2.]octane (*anti*-16d). *Anti*-**16d** was obtained as the major diastereomer in the reaction of **15** (240 mg, 0.65 mmol) with PhMgBr and purified by flash chromatography (silica gel, hexane/EtOAc: 6/1): 133 mg (0.30 mmol, 46%). Colorless solid, mp 144–146°C (from hexane). $[\alpha]_D^{23}=-55.5$ (c=1, $CHCl_3$). IR (KBr): 3460, 1450, 750, 690 cm^{-1}. ^1H NMR ($CDCl_3$): 0.89 (s, 3H, C*H*$_3$); 3.16 (d, 1H, J=9.2 Hz, C*H*N); 3.78 (br s, 1H, OH); 3.83 (d, 2H, J=13.8 Hz, C*H*HPh); 4.04 (s, 6H, C*H*$_2$O); 4.06 (d, 2H, J=13.8 Hz, CH*H*Ph); 5.00 (d, 1H, J=9.2 Hz, C*H*OH); 6.90–7.35 (m, 15H, H_{arom}). ^{13}C NMR ($CDCl_3$): 14.4 (*C*H$_3$); 30.3 (*C*CH$_3$); 54.8 (*C*H$_2$Ph); 63.9 (*C*HN); 71.9 (*C*H$_2$O); 73.5 (*C*HOH); 111.2 (*C*O$_3$); 126.3, 127.2, 127.7, 128.4, 129.2 (*C*H$_{arom}$); 139.7, 142.3 (C_{arom}). Anal. Calcd for $C_{28}H_{31}NO_4$: C, 75.48; H, 7.01; N, 3.14. Found: C, 75.62; H, 7.13; N, 3.23.

(2*S*, 3*R*)-3-Hydroxy norvaline (*ent*-*syn*-6). Compound *syn*-**16b** (80 mg, 0.2 mmol) was debenzylated over $Pd(OH)_2$ in MeOH as described for *syn*-**9** and stirred with 3 mL of 2N HCl solution in THF/H_2O (1/1) overnight at room temperature. The solvent was removed under reduced pressure and the residue was dissolved in dioxane/H_2O (2 mL) and treated with Na_2CO_3 (106 mg, 1 mmol) for 18 h at room temperature. The dioxane was removed, the mixture was extracted with ether, the aqueous layer was acidified with 2N HCl and then evaporated to dryness under vacuum to give (2*S*, 3*R*)-3-hydroxy norvaline hydrochloride. From this compound, the free β-hydroxy-α-amino acid was obtained by refluxing the salt in ethanol with excess propylene oxide followed by purification by flash chromatography (silica gel, CH_2Cl_2/CH_3OH/NH_4OH: 6/4/1), to give *ent*-*syn*-**6** as a colorless solid: 19 mg (0.14 mmol, 70%). Mp 230–232°C (dec). $[\alpha]_D^{23}=-7.6$ (c=0.9, H_2O).

(2*S*, 3*S*)-3-Hydroxy norvaline (*ent*-*anti*-6). Compound *anti*-**16b** (119 mg, 0.3 mmol) was deprotected as described for *syn*-**16b** to afford *ent*-*anti*-**6** as a colorless solid: 27 mg (0.2 mmol, 66%). Mp 222–223°C (dec). $[\alpha]_D^{23}=+4.4$ (c=0.8, H_2O).

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