Stereoselective cyclopropanation of serine- and threonine-derived oxazines to access new morpholine-based scaffolds†

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A general strategy for the synthesis of novel, orthogonally protected scaffolds based on the unique 2-oxa-5-azabicyclo[4.1.0]heptane structure is presented. The described reaction sequence takes advantage of easily available starting materials such as serine and threonine and leads to stereochemically dense structures in few, high-yielding synthetic steps. We show how the stereochemistry can be easily tuned by starting from different β-hydroxy-α-amino acids and also by means of a transition metal-catalyzed cyclopropanation step. The compounds find application as constrained templates for the construction of geometrically diversified libraries of compounds.

Introduction

One of the initial steps in the drug discovery process is the identification of leads which bind to receptors or other targets of interest. To address this, a common and established approach is the screening of libraries of compounds. While combinatorial chemistry initially tended towards the synthesis of very large libraries of structurally similar products, nowadays this initial emphasis on creating mixtures of very large numbers of structures is giving way to a more measured approach based on arrays of fewer, well-characterized compounds.[1] This is particularly noticeable in the move towards the synthesis of complex and highly diversified mixtures of molecules that bear a structural resemblance to approved natural-product-based drugs[2] or to "privileged medicinal scaffolds".[3] There is a strong drive towards the generation of new chemotypes, displaying increasing complexity and possessing features that can be related to pharmacologically relevant structures.[4] Among the possible alternatives, nitrogen-containing heterocycles with a saturated backbone have attracted considerable attention in the design of biologically active products.[5,6] Most marketed compounds and several promising leads fall into this category, and the discovery of small-molecular-weight scaffolds with a high degree of diversity belonging to this family is a tool of primary importance in the drug discovery process.[7] Among the various structures proposed by medicinal chemists, the morpholine ring represents a common motif.[8] Many carbon-substituted morpholines display biological activity and have found application as antidepressants,[9] appetite suppressants,[10] and antioxidants.[11] Some selected examples are shown in Fig. 1.

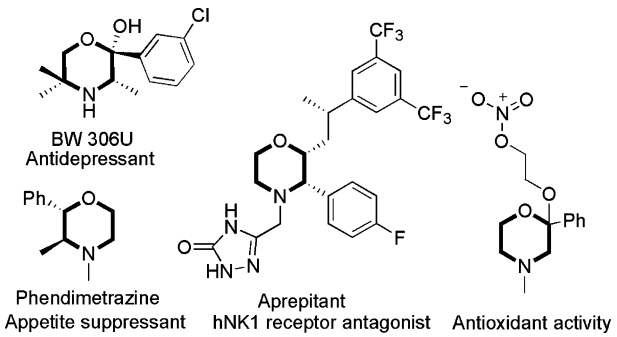
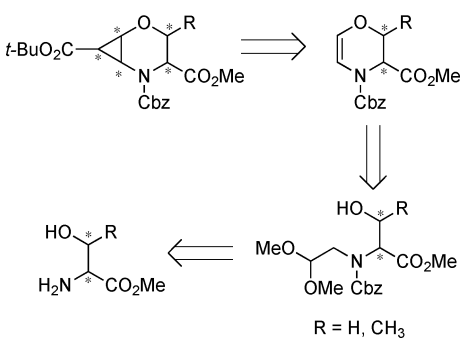


Fig. 1 Biologically relevant morpholine-based compounds.

During our ongoing research program toward the development of constrained, morpholine-based platforms for medicinal chemistry,[12] we developed the idea of rigidifying a chiral morpholine structure through fusion to a functionalized cyclopropane ring. This approach provides access to a stereochemically rich and rigid backbone, allowing us to generate different scaffolds by means of geometric variation of the scaffold itself.[13]

Herein we present the new template 2-oxa-5-azabicyclo-[4.1.0]heptane heterocycle (Scheme 1) and we demonstrate a general synthetic strategy which can guarantee the introduction of diversification positions with a high degree of diastereocontrol. The presence of oxygen and nitrogen atoms in the morpholine ring can be exploited in a wide range of retrosynthetic analyses[9] that allow easy control of the stereochemistry of the carbon atoms,



Scheme 1 Retrosynthetic analysis of 2-oxa-5-azabicyclo[4.1.0]heptane scaffolds.

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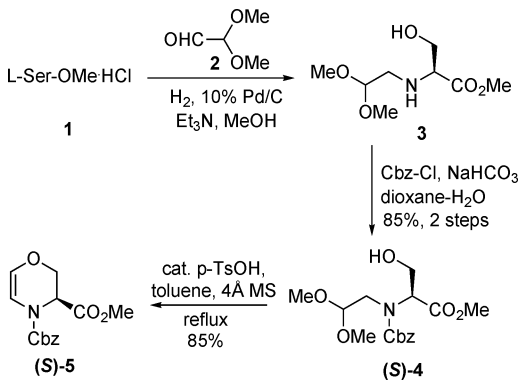
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of compounds **4**, **5**, **Cbz-8**, **10–13**, **14a**, **14b**, **15a**, **15b** and **18–20**; molecular modeling methods; total energies and cartesian coordinates of compound **20** (axial and equatorial conformers). See DOI: 10.1039/b808895k

especially starting from readily available amino acid derivatives. In order to obtain the 2-oxa-5-azabicyclo[4.1.0]heptane skeleton we planned to use amino acid-derived dihydrooxazine structures[14] (Scheme 1) as substrates for a diastereoselective, transition metal-catalyzed cyclopropanation using diazo-acetates. The cyclopropanation creates three new adjacent stereocenters and at the same time introduces a strong conformational constraint. This approach allows the synthesis of structures bearing functionalizable groups in different, reciprocal stereochemical relationships. Chirality is first introduced using readily available, enantiomerically pure β-hydroxy-α-amino acids as starting materials and is followed by a cyclopropanation step, whose stereochemical outcome is generally governed by the stereochemistry of the ligand used.

Results and discussion

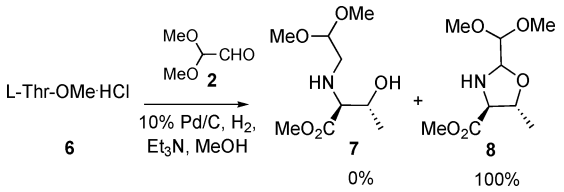
The strategy was developed using serine and threonine as starting materials and the Cbz as nitrogen protecting group. The serine-derived dihydroxazine **5** was prepared starting from amine **3**,[14] which was protected using Cbz-Cl and then cyclized in refluxing toluene upon treatment with *p*-TsOH and in the presence of 4 Å molecular sieves, in order to promote acid-catalyzed *trans*-acetalyzation and subsequent elimination of MeOH (Scheme 2).



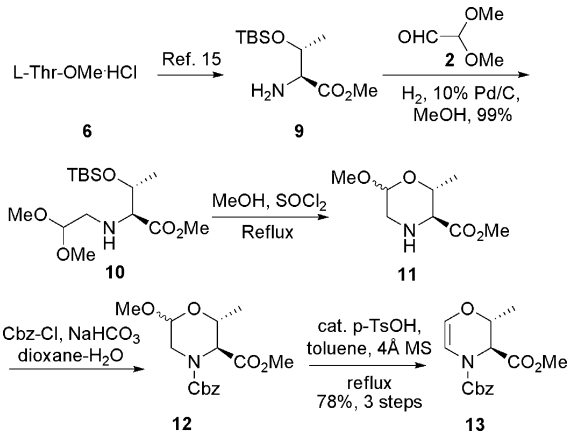
Scheme 2 Synthesis of serine-derived dihydroxazine **(*S*)-5**.

When this synthetic strategy was extended to threonine, problems initially arose in the reductive amination step with dimethoxyacetaldehyde. In fact, upon treatment of L-threonine methyl ester hydrochloride (**6**) with **2** and Pd/C in the presence of triethylamine and under a hydrogen atmosphere, the only observed product was not the expected **7**, but the oxazolidine **8** (Scheme 3).

Protection of the hydroxyl group of threonine with TBDMSCl[15] before performing the reductive amination was essential, and allowed the synthesis of **10** in almost quantitative yield (Scheme 4). Unfortunately, amine **10** was found to be completely unreactive



Scheme 3 Attempted synthesis of compound **7**.

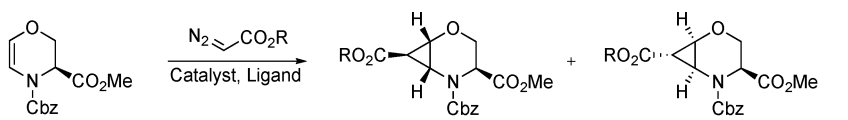


Scheme 4 Synthesis of threonine-derived dihydroxazine **13**.

upon treatment with Cbz-Cl under various reaction conditions. We reasoned that this poor reactivity was caused by high steric hindrance imposed by the TBDMS group, and thus amine **10** was subjected to harsher acid conditions, in order to deprotect the hydroxyl group and simultaneously obtain trans-acetalization. The amino group of the resulting cyclic acetal **11** proved to be much more reactive than **10**, and the crude product was easily protected upon treatment with Cbz-Cl/$NaHCO_3$ (aq). Subsequent treatment of cyclic acetal **12** with *p*-TsOH and 4 Å molecular sieves in refluxing toluene furnished the dihydroxazine scaffold **13** in good overall yield, requiring only one purification step by flash chromatography (Scheme 4).

We then focused our attention on the study of the cyclopropanation of the obtained dihydroxazine scaffolds using diazoacetates. Preliminary reactions using ethyl diazoacetate were carried out in order to establish the most effective metal catalyst and the best reaction conditions (Scheme 5 andTable 1, entries 1–4). We found that CuOTf (obtained *in situ* from $Cu(OTf)_2$ and phenylhydrazine) and $Rh_2(OAc)_4$ were both effective and gave comparable yields. Slow addition of ethyl diazoacetate was necessary to maintain a low "active carbene" concentration in solution, therefore preventing dimerization of the carbene itself.[16]

The best experimental conditions identified using ethyl diazoacetate were then extended to the cyclopropanation using *t*-butyl



Scheme 5 Cyclopropanation of dihydroxazine **(*S*)-5**.

Table 1 Experimental conditions for cyclopropanation of dihydroxazine **(*S*)-5**

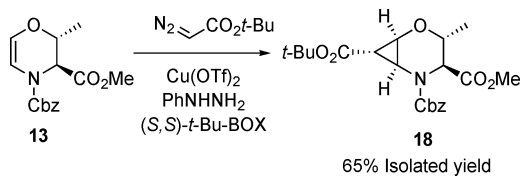
Entry	R	Catalyst	Ligand	EDA eq.	Time for diazoacetate addition	Combined yield **14** + **15**	Ratio[a] **14**:**15**
1	Et	$Rh_2(OAc)_4$	—	2	10 min	41%	1.6 : 1
2	Et	$Rh_2(OAc)_4$	—	3	5 h	72%	1.6 : 1
3	Et	$Cu(OTf)_2/PhNHNH_2$	—	3	5 h	75%	1.5 : 1
4	Et	$Cu(OTf)_2/PhNHNH_2$	—	4.5	6 h	86%	1.5 : 1
5	Et	$Cu(OTf)_2/PhNHNH_2$	(*S*,*S*)-*t*-BuBOX	4.5	6 h	73%	1 : 6
6	*t*-Bu	$Cu(OTf)_2/PhNHNH_2$	—	4.5	6 h	72%	1.4 : 1
7	*t*-Bu	$Cu(OTf)_2/PhNHNH_2$	(*S*,*S*)-*t*-BuBOX	4.5	5 h	67%	1 : 5
8	*t*-Bu	$Cu(OTf)_2/PhNHNH_2$	(*S*,*S*)-*t*-BuBOX	4.5	6 h	80%	1 : 6

[a] Estimated by ^{1}H-NMR.

diazoacetate, so as to obtain orthogonality with the methyl ester from the dihydroxazine. The introduction of a more hindered ester did not affect yield or diastereoselectivity (Table 1, entry 6), and cyclopropanation products could be isolated in good yield. Low diastereoselectivity between the two diastereomers **14** and **15** was observed, and only traces of the other two possible diastereomers were detected. Although diastereomers **14** and **15** could be separated by standard chromatography, the use of suitable chiral ligands was taken into account to enhance the diastereocontrol.

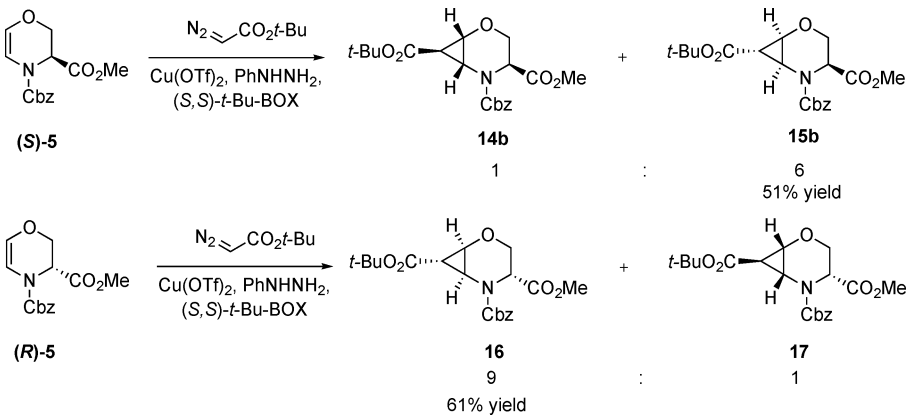
The bisoxazoline ligand (*S*,*S*)-2,2′-methylenebis(4-*t*-butyl-2-oxazoline), (*S*,*S*)-*t*-BuBOX),[17] proved to be effective when used in combination with copper(I) triflate. We observed that the stereochemistry of the cyclopropanes formed was mainly controlled by the ligand chirality, regardless of the stereochemistry of the dihydroxazine scaffold, suggesting in each case that the chiral ligand orients the attacking carbene to the same alkene face. In fact, when dihydroxazine **(*S*)-5** (derived from L-serine) was treated with *t*-butyl diazoacetate and (*S*,*S*)-*t*-BuBOX, the ratio between the diastereomers **14b** and **15b** was 1 : 6, whereas when the enantiomeric dihydroxazine (derived from D-serine) was used, the ratio of the two diastereomers **16**:**17** (enantiomeric to **14b** and **15b**, respectively) was reversed, giving a 9 : 1 mixture in favour of compound **16** (Scheme 6). Comparison of these data with the diastereomeric ratios obtained in the absence of the chiral ligand (Table 1, entries 3, 4 and 6) suggested that the combination of (*S*,*S*)-*t*-BuBOX with dihydroxazine **(*R*)-5** is the matched pair, whereas the same chiral ligand in combination with **(*S*)-5** is the mismatched pair.

Cyclopropanation of dihydroxazine **13**, derived from L-threonine methyl ester **6**, with (*S*,*S*)-*t*-BuBOX and *t*-butyl diazoacetate resulted in compound **18** as the major stereoisomer and only traces of a second stereoisomer (Scheme 7), indicating an additional effect of the methyl group at C-2 of dihydroxazine **13** on the stereoselectivity.



Scheme 7 (*S*,*S*)-*t*-BuBOX–Cu(OTf)-catalyzed cyclopropanation of dihydroxazine **13**.

The structural assignment of the diastereomers **14a/b**, **15a/b** and **18** was accomplished by analyzing the values of the coupling constants between the hydrogen atoms in the cyclopropane ring and by means of NOE experiments. We used the relationship that coupling constants less than 7 Hz are associated with a *trans* relationship between two protons in a cyclopropane ring.[18] In all the diastereomeric bicyclic compounds isolated, *J* couplings of H-7 with the other two protons of the cyclopropane ring (H-1 and H-6) were 2.4–3.6 Hz, indicating a *trans* relationship between

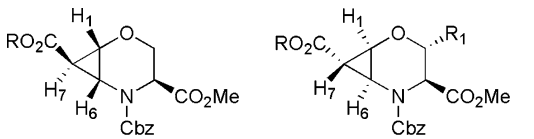


Scheme 6 (*S*,*S*)-*t*-BuBOX–CuOTf-catalyzed cyclopropanation of dihydroxazines **(*S*)-** and **(*R*)-5**.

Table 2 Vicinal coupling constants for the hydrogens of the cyclopropane ring in the scaffolds **14** and **15**

Compd	$J_{6,7}$/Hz	$J_{1,7}$/Hz	$J_{1,6}$/Hz
14a	3.2	3.2	7.2
14b	3.6	2.4	7.2
15a	3.6	2.4	7.2
15b	3.2	3.2	7.2
18	3.2	3.2	7.2

the H-7 and H-1/H-6 protons, and consequently a *cis* relationship between H-1 and H-6. (Fig. 2 and Table 2).



14a, R = Et
14b, R = *t*-Bu

15a, R = Et, R_1 = H
15b, R = *t*-Bu, R_1 = H
18, R = *t*-Bu, R_1 = CH_3

Fig. 2 Scaffolds **14**, **15** and **18**.

A definitive structure elucidation was based on NOE spectra for the bicyclic morpholine-based scaffolds deriving from cyclopropanation with *t*-butyl diazoacetate. In particular, a diagnostic NOE effect between H-4 and H-7 was observed for compound **14b** (Fig. 3). For compound **15b**, H-7 provided only a weak NOE effect with the methyl ester protons at C-4, and a strong NOE effect was observed between H-7 and one of the two methylenic protons at C-3 of the morpholine ring (Fig. 3). NOE spectra of compound **18** deriving from L-threonine resulted in NOE interactions between the protons of the methyl group at C-3 and the two protons H-1 and H-6. This strongly supported the structure in Fig. 3, with the two esters in a *trans* relationship.

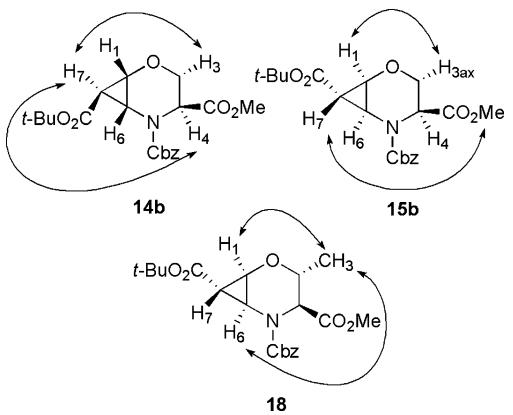


Fig. 3 Most significant NOEs observed for structures **14b**, **15b** and **18**.

Molecular modeling calculations were carried out on compound **18** so as to assess the most stable conformation and to gain insight into the detailed structure of the bicyclic scaffold. Energy-minimized conformations of the 2-oxa-5-azabicyclo[4.1.0]heptane-based scaffold **18** were achieved using SPARTAN Version 5.1[19] running on a SGI IRIX 6.5 workstation. Conformational searches of **18** were carried out using a Monte Carlo method within the MMFF94 force field,[20] and the AM1 semiempirical method[21] was used to optimize the global minimum conformer. The geometries of the most abundant minimum energy conformers were successively subjected to *ab initio* single-point energy calculation at the 3-21G*/HF level[22] of quantum chemical theory. The conformation having axial C-2 and C-3 substituents resulted in a twisted half-chair structure for the morpholine moiety, whereas a twisted half-boat structure was obtained for the conformation having the same substitutents in equatorial position. Also, the conformation with axial C-2 and C-3 substituents proved to be more stable by about 2.3 kcal mol^{-1} (E_{ax} = −232.14 kcal mol^{-1}; E_{eq} = −229.86 kcal mol^{-1}). Computation of the dihedral angle formed by H-2, C-2, C-3, H-3 atoms for the axial and equatorial conformations resulted in −73.6° and −144.6°, respectively, which, in conjunction with ^{1}H-NMR data indicating absence of coupling between H-2 and H-3, suggested the axial conformer as the more favourable in chloroform solution (Fig. 4).

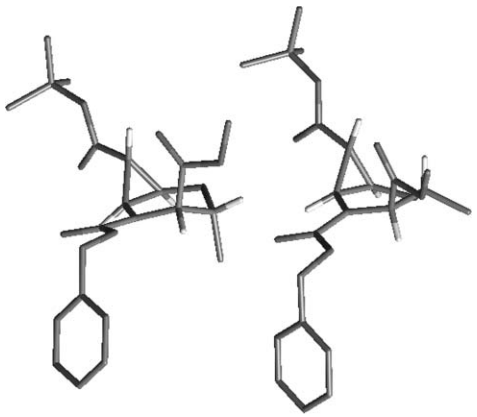


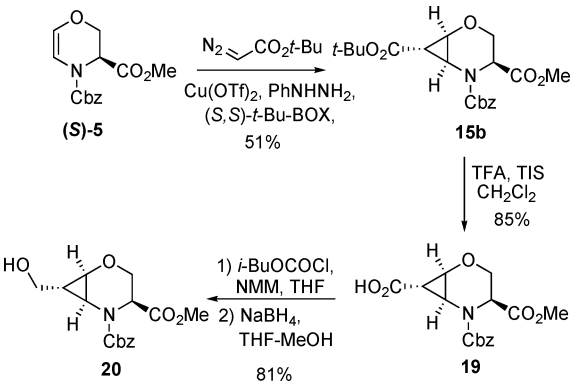
Fig. 4 Energy-minimized conformations of **18** bearing axial (left) and equatorial (right) substituents at C-2 and C-3.

Further corroboration of the preferential axial conformation for **18** was given by NOE experiments, which showed NOE correlation of H-7 with methyl ester protons (and not H-2), and of H-6 with the methyl group at C-2.

In order to extend the versatility of the bicyclic structures reported herein, the selective transformation of the *t*-butyl ester into a primary alcohol using compound **15b** as substrate was carried out. Specifically, the orthogonality of the two esters was used for selective deprotection of the *t*-butyl ester under standard acid conditions, followed by reduction of the resulting acid with isobutyl chloroformate/$NaBH_4$ (Scheme 8). Both transformations proved to be completely stereoselective, and no epimerization at C-7 was observed by ^{1}H-NMR, giving the corresponding alcohol **20** in overall 69% yield from **18**, and demonstrating the feasibility of such scaffold as a template for subsequent appendage diversity.

Conclusions

In summary we have developed an efficient strategy which gives access to a new series of scaffolds based on the unique heterocyclic structure of the 2-oxa-5-azabicyclo[4.1.0]heptane. The strategy allows the generation of compounds with up to five stereogenic centers in enantiopure form starting from readily available β-hydroxy-α-amino acids and by means of a diastereoselective cyclopropanation achieved using diazoacetates in conjunction with



Scheme 8 Synthesis of compound **20**.

Cu(I)OTf and a chiral *t*-BuBOX ligand. The cyclopropanation outcome proved to be mainly controlled by the stereochemistry of the bis-isooxazolidine ligand. A variety of scaffolds can be obtained using this strategy, each of them differing for the spatial orientation of the orthogonally protected diversification sites. Some final manipulations of the synthesized structures have been presented, in order to prove the versatility and the orthogonal relationship between the various protecting groups introduced.

Experimental

Chromatographic separations were performed on silica gel using flash-column techniques. R_f values refer to TLC carried out on 25 mm silica gel plates (Merck F254) with the same eluant as for column chromatography. ^{1}H and ^{13}C NMR spectra were recorded with NMR instruments operating at 200 MHz and 400 MHz for proton and at 50 MHz for carbon, and using $CDCl_3$ solutions unless otherwise stated. EI mass spectra were carried out at 70 eV ionizing voltage.

(*S*)-2-[Benzyloxycarbonyl-(2,2-dimethoxyethyl)amino]-3-hydroxypropionic acid methyl ester [(*S*)-4]

L-Serine methyl ester hydrochloride (**1**) (5.34 g, 34.3 mmol) was dissolved in MeOH (110 mL), then triethylamine (4.79 mL, 34.3 mmol), 60% aqueous solution of dimethoxyacetaldehyde (**2**) (5.95 g, 34.3 mmol) and 10% Pd/C (477 mg) were successively added, and the resulting mixture was stirred overnight at room temperature under a hydrogen atmosphere. Then, the suspension was filtered over Celite and the organic solvent was removed under reduced pressure. The crude reaction mixture was dissolved in H_2O (60 mL), and $NaHCO_3$ (5.76 g, 68.6 mmol) was added. EtOAc (75 mL) was added and the mixture was cooled at 0 °C with an ice bath. Cbz-Cl (4.80 mL, 33.61 mmol) was added dropwise, then, after 1 h stirring, the ice bath was removed and the mixture was stirred overnight. The reaction was diluted with EtOAc (200 mL) and the aqueous layer was discarded. The organic phase was washed with 1 M HCl, brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (EtOAc–hexanes 3 : 2) to provide compound **(*S*)-4** as a colourless oil (10.01 g, 85%). (Found: C, 56.40; H, 6.95; N 4.01. $C_{16}H_{23}NO_7$ requires C, 56.30; H, 6.79; N, 4.10%); $[\alpha]_D^{26}$ −42.9 (*c* 1.0, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 1 : 1 mixture of rotamers 7.36–7.29 (m, 5 H, *Ph*), 5.21 (AB, part A, J = 6.0 Hz, 0.5 H, CH_2Ph), 5.13 (s, 1 H, CH_2Ph), 5.13 (AB, part B, J = 6.0 Hz, 0.5 H, CH_2Ph), 4.70 (dd, J = 7.2, 4.0 Hz, 0.5 H), 4.65–4.58 (m, 1 H), 4.49 (dd, J = 7.2, 4.0 Hz, 0.5 H), 4.05–3.77 (m, 2 H), 3.71 (s, 1.5 H, CO_2CH_3), 3.58 (s, 1.5 H, CO_2CH_3), 3.68–3.54 (m, 2 H) 3.45 (s, 1.5 H, OCH_3), 3.43 (s, 1.5 H, OCH_3), 3.31 (s, 1.5 H, OCH_3), 3.28 (s, 1.5 H, OCH_3), 3.26–3.21 (m, 1 H); δ_C (50 MHz; $CDCl_3$) mixture of rotamers 170.0 (s, CO_2CH_3), 156.3 and 156.1 (s, NCO_2), 135.7 (s, *i-Ph*), 128.2–127.6 (d, 5 C, *Ph*), 103.5 and 102.9 [d, $CH(OCH_3)_2$], 67.7 and 67.5 (t, PhCH_2), 62.8 and 62.3 (d, N*C*H), 60.7 and 60.4 (t, CH_2OH), 55.1 and 54.8 (q, CO_2CH_3), 54.3 and 52.0 (q, 2 C, OCH_3), 49.2 (t, NCH_2); MS *m*/*z* 309 (M^+ − CH_3OH, 1.9), 277 (0.7), 264 (0.7), 250 (0.6), 234 (0.5), 220 (0.1), 91 (100).

(*R*)-2-[Benzyloxycarbonyl-(2,2-dimethoxyethyl)amino]-3-hydroxypropionic acid methyl ester [(*R*)-4]

Compound **(*R*)-4** was prepared as for **(*S*)-4** starting from D-serine methyl ester hydrochloride and (**2**), with identical NMR data to the enantiomeric compound **(*S*)-4**. (Found: C, 56.20; H, 6.84; N 4.02. $C_{16}H_{23}NO_7$ requires C, 56.30; H, 6.79; N, 4.10%); $[\alpha]_D^{25}$ +41.7 (*c* 1.0, $CHCl_3$).

(*S*)-2,3-Dihydro-[1,4]oxazine-3,4-dicarboxylic acid 4-benzyl ester 3-methyl ester [(*S*)-5]

A solution of compound **(*S*)-4** (1.12 g, 3.28 mmol) in toluene (45 mL) containing a catalytic amount of *p*-toluenesulfonic acid monohydrate (63 mg, 0.33 mmol) was placed in a single-necked round-bottomed flask equipped with a reflux condenser and a dropping funnel containing approximately 16 g of 4 Å molecular sieves. The mixture was refluxed for 2.5 h, then cooled to room temperature and filtered through a thin layer of $NaHCO_3$. Toluene was removed under reduced pressure, and the crude product was purified by flash column chromatography (hexanes–EtOAc 3 : 1) to yield compound **(*S*)-5** as a colourless oil (729 mg, 78%). (Found: C, 60.81; H, 5.55; N, 5.01. $C_{14}H_{15}NO_5$ requires C, 60.64; H, 5.45; N, 5.05%); $[\alpha]_D^{25}$ +8.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3 : 2 mixture of rotamers α and β 7.39–7.30 (m, 5 H, *Ph*), 6.45 (d, J = 2.4 Hz, 0.4 H, *H*-6 β), 6.33 (d, J = 2.6 Hz, 0.6 H, *H*-6 α), 6.03 (d, J = 2.4 Hz, 0.4 H, *H*-5 β), 5.90 (d, J = 2.6 Hz, 0.6 H, *H*-5 α), 5.29–5.15 (m, 2 H, CH_2Ph), 4.95 (s, 0.6 H, *H*-2 α), 4.83 (s, 0.4 H, *H*-2 β), 4.65 (dd, J = 10.8, 0.8 Hz, 0.6 H, *H*-2 α), 4.57 (d, J = 10.8, 0.8 Hz, 0.4 H, *H*-2 β), 3.97–3.92 (m, 1 H, *H*-3), 3.78 (s, 1.8 H, OCH_3 α), 3.71 (s, 1.2 H, OCH_3 β); δ_C (50 MHz, $CDCl_3$) mixture of rotamers 168.2 and 168.0 (s, CO_2CH_3), 151.7 and 151.0 (s, NCO_2), 135.4 (s, *i-Ph*), 129.4 and 128.2 (d, *C*-6), 128.1–127.6 (d, 5 C, *Ph*), 105.8 and 105.3 (d, *C*-5), 67.7 and 67.5 (t, CH_2Ph), 65.1 and 64.7 (t, *C*-2), 54.4 (q, CO_2CH_3), 53.7 and 52.5 (d, *C*-3); MS *m*/*z* 277 (M^+, 4), 249 (11), 91 (100).

(*R*)-2,3-Dihydro-[1,4]oxazine-3,4-dicarboxylic acid 4-benzyl ester 3-methyl ester [(*R*)-5]

Compound **(*R*)-5** was prepared as for **(*S*)-5** starting from **(*R*)-4**, with identical NMR data to the enantiomeric compound **(*S*)-5**. (Found: C, 60.78; H, 5.51; N, 5.09. $C_{14}H_{15}NO_5$ requires C, 60.64; H, 5.45; N, 5.05%); $[\alpha]_D^{25}$ −7.2 (*c* 2.5, $CHCl_3$).

(2*R*/*S*,4*S*,5*R*)-2-Dimethoxymethyl-5-methyloxazolidine-4-carboxylic acid methyl ester (8): synthesis of the Cbz-protected derivative of 8

Compound **8** was obtained as a by-product starting from L-threonine methyl ester (**6**) (2.42 g, 14.3 mmol) according to the reported procedure for the preparation of **4** (see ref. 14). The crude product **8** was then characterized as the corresponding Cbz-protected derivative, after treatment of crude **8** with Cbz-Cl according to procedure as for **4**. Pure Cbz-protected compound (2.76 g, 12.4 mmol) was obtained after chromatographic purification (hexanes–EtOAc 1 : 3) in 87% yield over two steps. (Found: C, 57.96; H, 6.61; N, 3.74. $C_{17}H_{23}NO_7$ requires C, 57.78; H, 6.56; N, 3.96%); δ_H (200 MHz, $CDCl_3$) mixture of diastereomers 7.31 (m, 5 H, *Ph*), 5.31 [s, 1 H, C*H*(OCH$_3$)$_2$], 5.15 (s, 2 H, CH_2Ph), 4.58 (m, 1 H, OC*H*N), 4.46 (m, 1 H, C*H*CH$_3$), 4.07 (m, 1 H, NC*H*CO$_2$), 3.69 (s, 3 H, CO$_2$CH_3), 3.46 (s, 6 H, OCH_3), 1.39 (d, $J = 5.6$ Hz, 3 H, CHCH_3); δ_C (50 MHz, $CDCl_3$) mixture of diastereomers 169.6 (s, *C*O$_2$CH$_3$), 135.6 (s, *i-Ph*), 128.2 (d, 2 C, *Ph*), 127.9 (d, 2 C, *Ph*), 127.5 (d, *Ph*), 104.2 [d, *C*H(OCH$_3$)$_2$], 88.6 (d, O*C*HN), 67.5 (t, *C*H$_2$Ph), 64.4 (d, *C*HCH$_3$), 55.7 (d, N*C*HCO$_2$), 52.3 (q, CO$_2$*C*H$_3$), 19.5 (q, CH*C*H$_3$).

(2*S*,3*R*)-3-(*t*-Butyldimethylsilanyloxy)-2-(2,2-(dimethoxy)ethylamino)butyric acid methyl ester (10)

Compound **9** (3.70 g, 14.9 mmol) was dissolved in MeOH (45 mL), then 60% aqueous solution of dimethoxyacetaldehyde (**2**) (2.59 g, 14.9 mmol) and 10% Pd/C (329 mg) were successively added, and the resulting mixture was stirred overnight at room temperature under a hydrogen atmosphere. Then, the suspension was filtered on Celite and MeOH was removed under reduced pressure. The resulting mixture was partitioned between water and Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to yield compound **10** as a colourless oil (4.95 g, 99%). (Found: C, 53.86; H, 10.00; N, 4.22. $C_{15}H_{33}NO_5Si$ requires C, 53.70; H, 9.91; N, 4.17%); $[\alpha]_D^{25}$ −11.4 (*c* 1.1, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 4.53 [t, $J = 5.2$ Hz, 1 H, C*H*(OCH$_3$)$_2$], 4.18 (qui, $J = 5.3$ Hz, 1 H, OC*H*CH$_3$), 3.73 (s, 3 H, CO$_2$CH_3), 3.37 (s, 6 H, OCH_3), 3.37 (m, 1 H, NC*H*CO$_2$), 2.94 (dd, $J = 12.2$, 5.8 Hz, 1 H, CH_2CH), 2.73 (dd, $J = 12.2$, 5.0 Hz, 1 H, CH_2CH), 1.25 (d, $J = 6.4$ Hz, 3 H, CHCH_3), 0.85 [s, 9 H, (CH_3)$_3$CSi], 0.44 (s, 3 H, CH_3Si), 0.14 (s, 3 H, CH_3Si); δ_C (50 MHz, $CDCl_3$) 171.9 (s, *C*O$_2$CH$_3$), 102.9 [d, *C*H(OCH$_3$)$_2$], 69.1 (d, O*C*HCH$_3$), 66.8 (d, N*C*HCO$_2$), 54.4 (q, O*C*H$_3$), 53.6 (q, O*C*H$_3$), 52.0 (q, CO$_2$*C*H$_3$), 48.9 (t, *C*H$_2$CH), 25.7 [q, 3 C, (*C*H$_3$)$_3$CSi], 20.8 (q, CH*C*H$_3$), 17.9 [s, (CH$_3$)$_3$*C*Si], −4.2 (q, *C*H$_3$Si), −5.1 (q, *C*H$_3$Si); MS *m*/*z* 304 (M$^+$ − CH$_3$O, 8), 291 (15), 278 (6), 246 (13), 159 (38), 73 (100).

(2*R*,3*S*,6*R*/*S*)-6-Methoxy-2-methylmorpholine-3-carboxylic acid methyl ester (11)

$SOCl_2$ (511 μL, 7 mmol) was added dropwise, at 0 °C, to 7 mL of MeOH. The resulting solution was used to dissolve compound **10** (600 mg, 1.79 mmol). The resulting mixture was refluxed for 4 h, and then concentrated under reduced pressure. The crude material was dissolved again in MeOH, neutralized with Amberlyst A-21, and the solvent was evaporated to dryness. The product was directly used without further purification for the subsequent protection step. An analytically pure sample was obtained after purification by flash column chromatography (EtOAc). (Found: C, 50.86; H, 8.08; N, 7.22. $C_8H_{15}NO_4$ requires C, 50.78; H, 7.99; N, 7.40%); δ_H (400 MHz, $CDCl_3$) 3 : 2 mixture of diastereomers α and β 4.47 (s, 0.4 H, *H*-6 β), 4.40 (dd, $J = 8.8$, 2.4 Hz, 0.6 H, *H*-6 α), 3.88 (qd, $J = 5.0$, 1.8 Hz, 0.4 H, *H*-2 β), 3.74 and 3.73 (s, 3 H, CO$_2$CH_3), 3.65 (qd, $J = 4.2$, 1.2 Hz, 0.6 H, *H*-2 α), 3.50 (s, 1.8 H, OCH_3 α), 3.39 (s, 1.2 H, OCH_3 β), 3.27 (d, $J = 9.4$ Hz, 0.4 H, *H*-3 β), 3.18 (d, $J = 9.4$ Hz, 0.6 H, *H*-3 α), 3.04 (dd, $J = 12.4$, 2.4 Hz, 0.6 H, *H*-5 α), 2.92–2.90 (m, 0.8 H, *H*-5 β), 2.59 (dd, $J = 12.4$, 8.8 Hz, 0.6 H, *H*-5 α), 1.75–1.95 (br, 1 H, N*H*), 1.25 (d, $J = 6.4$ Hz, 1.8 H, CHCH_3 α), 1.15 (d, $J = 6.0$ Hz, 1.2 H, CHCH_3 β); δ_C (50 MHz, $CDCl_3$) mixture of diastereomers 171.1 (s, *C*O$_2$CH$_3$), 100.6 and 95.6 (d, *C*-6), 73.7 and 65.4 (d, *C*-2), 63.6 and 62.8 (d, *C*-3), 56.1 and 54.5 (q, O*C*H$_3$), 52.1 (q, CO$_2$*C*H$_3$), 47.9 and 47.2 (t, *C*-5), 18.2 (q, CH*C*H$_3$).

(2*R*,3*S*,6*R*/*S*)-6-Methoxy-2-methylmorpholine-3,4-dicarboxylic acid 4-benzyl ester 3-methyl ester (12)

Crude cyclic acetal **11** was dissolved in H_2O (5 mL) and $NaHCO_3$ (297 mg, 3.54 mmol) was added. The mixture was stirred until complete dissolution of the salt, then dioxane (8 mL) was added. The flask was cooled at 0 °C with an ice bath and Cbz-Cl (253 mg, 1.77 mmol) was added dropwise. After 10 minutes the ice bath was removed and the reaction mixture was stirred for 1 day at room temperature. Afterwards, EtOAc (25 mL) and water (10 mL) were added. The aqueous layer was discarded and the organic phase was washed with 1 M HCl, brine, and dried over Na_2SO_4. The solvent were removed under reduced pressure, and the crude material was used without purification for the elimination reaction. An analytically pure sample was obtained after purification by flash column chromatography (hexanes–EtOAc 3 : 1). (Found: C, 59.77; H, 6.78; N, 4.24. $C_{16}H_{21}NO_6$ requires C, 59.43; H, 6.55; N, 4.33%); δ_H (400 MHz, $CDCl_3$) mixture of diastereomers, mixture of rotamers 7.34–7.25 (m, 5 H, Ph), 5.23–5.01 (m, 2 H, CH_2Ph), 4.82–4.78 (m, 1 H, *H*-6), 4.70–4.63 (m, 1 H, *H*-2), 4.32–4.10 (m, 2 H, *H*-3 and *H*-5), 3.98–3.42 (m, 3 H, CO$_2$CH_3), 3.42–3.38 (m, 3 H, OCH_3), 1.43–1.35 (m, 3 H, CHCH_3); δ_C (50 MHz, $CDCl_3$) mixture of diastereomers, mixture of rotamers 170.2 (s, *C*O$_2$CH$_3$), 135.9 (s, *i-Ph*), 128.3–127.6 (d, 5 C, *Ph*), 97.0 (d, *C*-6), 69.1 (d, *C*-2), 67.6 (t, *C*H$_2$Ph), 59.5 (d, *C*-3), 55.3 (q, O*C*H$_3$), 52.3 (q, CO$_2$*C*H$_3$), 44.3 (t, *C*-5), 20.0 and 18.9 (q, CH*C*H$_3$).

(2*R*,3*S*)-2-Methyl-2,3-dihydro-[1,4]oxazine-3,4-dicarboxylic acid 4-benzyl ester 3-methyl ester (13)

Crude protected acetal **12** was dissolved in toluene (10 mL) containing a catalytic amount of *p*-toluenesulfonic acid monohydrate (34 mg, 0.18 mmol) and placed in a single-necked round-bottomed flask equipped with a reflux condenser and a dropping funnel containing approximately 10 g of 4 Å molecular sieves. The mixture was refluxed for 2 h, then cooled to room temperature and filtered through a thin layer of $NaHCO_3$. Toluene was removed under reduced pressure, and the crude product was purified by flash column chromatography (hexanes–EtOAc 7:2) to yield compound **13** as colourless oil (406 mg, 78% over 3 steps from compound **10**). (Found: C, 61.80; H, 6.01; N, 4.91. $C_{15}H_{17}NO_5$ requires C, 61.85;

H, 5.88; N, 4.81%); $[\alpha]_D^{26}$ −7.2 (*c* 0.2, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 3 : 2 mixture of rotamers α and β 7.39–7.30 (m, 5 H, *Ph*), 6.39 (d, $J = 4.8$ Hz, 0.4 H, *H*-6 β) 6.27 (d, $J = 4.8$ Hz, 0.6 H, *H*-6 α), 5.88 (d, $J = 4.8$ Hz, 0.4 H, *H*-5 β) 5.75 (d, $J = 4.8$ Hz, 0.6 H, *H*-5 α), 5.25 (AB, part A, $J = 12$ Hz, 0.4 H, CH_2Ph β), 5.24 (s, 1.2 H, CH_2Ph α), 5.16 (AB, part B, $J = 12$ Hz, 0.4 H, CH_2Ph β), 4.83 (qd, $J = 6.4$, 1.2 Hz, 0.6 H, *H*-2 α), 4.72 (qd, $J = 6.4$, 1.2 Hz, 0.4 H, *H*-2 β), 4.68 (s, 0.6 H, *H*-3 α), 4.55 (s, 0.4 H, *H*-3 β), 3.77 (s, 1.8 H, CO_2CH_3 α), 3.69 (s, 1.2 H, CO_2CH_3 β), 1.31 (d, $J = 6.4$ Hz, 1.8 H, $CHCH_3$ α) 1.30 (d, $J = 6.4$ Hz, 1.2 H, $CHCH_3$ β); δ_C (50 MHz, $CDCl_3$) mixture of rotamers 168.4 (s, CO_2CH_3), 152.8 (s, NCO_2), 135.6 (s, *i-Ph*), 128.4–127.7 (d, 5 C, *Ph*), 126.8 and 125.7 (d, *C*-6), 104.7 and 104.3 (d, *C*-5), 69.7 and 69.1 (d, *C*-2), 68.0 and 67.7 (t, CH_2Ph), 58.1 and 57.3 (d, *C*-3), 52.6 (q, CO_2CH_3), 17.2 (q, $CHCH_3$); MS *m*/*z* 291 (M^+, 4.6), 188 (15.9), 91 (100).

Cyclopropanation with $Cu(OTf)_2$ and (*S*,*S*)-2,2′-isopropylidene-bis(4-*t*-butyl-2-oxazoline): general procedure A

To a solution of dihydroxazine **5** (626 mg, 2.24 mmol) in dry CH_2Cl_2 (4 mL) cooled in an ice–salt bath were added $Cu(OTf)_2$ (16 mg, 0.045 mmol), (*S*,*S*)-2,2′-isopropylidene-bis(4-*t*-butyl-2-oxazoline) (16 mg, 0.056 mmol) and phenylhydrazine (4.4 μL, 0.045 mmol). After 30 min, a 1.2 M solution of diazoacetate in dry CH_2Cl_2 was added (quantity and time according to Table 1). The reaction was then gently warmed to room temperature and stirred for 16 h. Then, the mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (hexanes–EtOAc 3 : 1) to yield the cyclopropanated products.

Cyclopropanation with $Cu(OTf)_2$, without chiral ligand: general procedure B

To a solution of dihydroxazine scaffold (417 mg, 1.49 mmol) in dry CH_2Cl_2 (3 mL) cooled in an ice–salt bath were added $Cu(OTf)_2$ (11 mg, 0.030 mmol) and phenylhydrazine (2.9 μL, 0.030 mmol). After 30 min, a 1.2 M solution of diazoacetate in dry CH_2Cl_2 was added (quantity and time according to Table 1). The reaction was then gently warmed to room temperature and stirred for 16 h. Then, the mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (hexanes–EtOAc 3 : 1) to yield the cyclopropanated products.

Cyclopropanation with $Rh_2(OAc)_4$: general procedure C

To a solution of dihydroxazine scaffold (522 mg, 1.87 mmol) in dry CH_2Cl_2 (4 mL) cooled in an ice–salt bath $Rh_2(OAc)_4$ (2.5 mol%), and a 1.2 M solution of diazoacetate in dry CH_2Cl_2 was added (quantity and time according to Table 1). The reaction was then gently warmed to room temperature and stirred for 16 h. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (hexanes–EtOAc 3 : 1) to yield the cyclopropanated products.

(1*S*,4*S*,6*R*,7*R*)-2-Oxa-5-azabicyclo[4.1.0]heptane-4,5,7-tricarboxylic acid 5-benzyl ester 7-ethyl ester 4-methyl ester (14a)

626 mg (2.24 mmol) of compound **(*S*)-5** were treated according to general procedure A using 4.5 equivalents of ethyl diazoacetate (6 h time of addition) to yield 81 mg (10%) of 14a as the minor stereoisomer, or in higher amounts according to general procedure B. (Found: C, 60.02; H, 5.71; N, 3.70. $C_{18}H_{21}NO_7$ requires C, 59.50; H, 5.83; N, 3.85%); $[\alpha]_D^{25}$ −48.1 (*c* 1.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2 : 1 mixture of rotamers α and β 7.35–7.29 (m, 5 H, *Ph*), 5.29 (AB, part A, $J = 12.5$ Hz, 0.66 H, CH_2Ph α), 5.17 (AB, part B, $J = 12.5$ Hz, 0.66 H, CH_2Ph α), 5.24–5.11 (m, 0.66 H, CH_2Ph β), 4.47 (t, $J = 4.8$ Hz, 0.66 H, *H*-4 α), 4.19 (t, $J = 4.8$ Hz, 0.33 H, *H*-4 β), 4.20–4.03 (m, 3 H, $CO_2CH_2CH_3$ and *H*-1), 4.03 (dd, $J = 11.6$, 5.2 Hz, 0.66 H, *H*-3 α), 3.94 (dd, $J = 11.6$, 5.2 Hz, 0.33 H, *H*-3 β), 3.84 (dd, $J = 11.6$, 4.8 Hz, 1 H, *H*-3), 3.78 (s, 2 H, CO_2CH_3 α), 3.67 (s, 1 H, CO_2CH_3 β), 3.54–3.49 (m, 1 H, *H*-6), 2.00 (t, $J = 3.2$ Hz, 1 H, *H*-7), 1.98 (t, $J = 7.2$ Hz, 2 H, $CO_2CH_2CH_3$); δ_C (50 MHz, $CDCl_3$) mixture of rotamers 169.4 (s, CO_2), 169.2 (s, CO_2), 155.9 (s, NCO_2), 135.7 (s, *i-Ph*), 128.2–127.1 (d, 5 C, *Ph*), 67.8 and 67.7 (t, CH_2Ph), 64.6 and 64.1 (t, *C*-3), 60.7 (t, $CO_2CH_2CH_3$), 59.1 (d, *C*-1) 53.1 and 52.6 (d, *C*-4) 52.0 (q, CO_2CH_3), 33.9 (d, *C*-6), 26.4 and 26.0 (d, *C*-7), 14.2 (q, $CO_2CH_2CH_3$); MS *m*/*z* 363 (M^+, 0.8), 318 (0.2), 290 (2), 228 (15), 182 (18), 91 (100).

(1*S*,4*S*,6*R*,7*R*)-2-Oxa-5-azabicyclo[4.1.0]heptane-4,5,7-tricarboxylic acid 5-benzyl ester 7-*t*-butyl ester 4-methyl ester (14b)

Compound **14b** was obtained from **(*S*)-5** as the minor diastereomer according to general procedure A, or in higher amounts according to general procedure B. (Found: C, 61.06; H, 6.71; N, 3.55. $C_{20}H_{25}NO_7$ requires C, 61.37; H, 6.44; N, 3.58%); $[\alpha]_D^{25}$ −61.3 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2 : 1 mixture of rotamers α and β 7.38–7.28 (m, 5 H, *Ph*), 5.28 (AB, part A, $J = 12.4$ Hz, 0.66 H, CH_2Ph α), 5.24 (AB, part A, $J = 7.9$ Hz, 0.33 H, CH_2Ph β), 5.14 (AB, part B, $J = 12.4$ Hz, 0.66 H, CH_2Ph α), 5.10 (AB, part B, $J = 8.0$ Hz, 0.33 H, CH_2Ph β), 4.45 (t, $J = 4.8$ Hz, 0.66 H, *H*-4 α), 4.38 (t, $J = 4.8$ Hz, 0.33 H, *H*-4 β), 4.10 (m, 0.33 H, *H*-1 β), 4.09 (dd, $J = 7.2$, 3.2 Hz, 0.66 H, *H*-1 α), 3.94 (dd, $J = 11.6$, 3.2 Hz, 0.66 H, *H*-3 α), 3.90 (dd, $J = 11.6$, 4.8 Hz, 0.33 H, *H*-3 β), 3.82 (dd, $J = 11.6$, 4.8 Hz, 1 H, *H*-3), 3.77 (s, 2 H, CO_2CH_3 α), 3.65 (s, 1 H, CO_2CH_3 β), 3.47 (dd, $J = 7.2$, 3.2 Hz, 0.33 H, *H*-6 β), 3.42 (dd, $J = 7.2$, 3.2 Hz, 0.66 H, *H*-6 α), 1.92 and 1.89 (t, $J = 3.2$ Hz, 1 H, *H*-7), 1.43 [s, 3 H, $CO_2C(CH_3)_3$ β], 1.37 [s, 6 H, $CO_2C(CH_3)_3$ α]; δ_C (50 MHz, $CDCl_3$) mixture of rotamers 169.4 (s, CO_2), 168.1 (s, CO_2), 156.0 (s, NCO_2), 135.6 (s, *i-Ph*), 128.3–127.2 (d, 5 C, *Ph*), 81.0 [s, $C(CH_3)_3$], 67.8 (t, CH_2Ph), 64.5 and 64.1 (t, *C*-3), 58.8 (d, *C*-1), 53.1 (d, *C*-4), 52.6 (d, *C*-6) 52.1 (q, CO_2CH_3), 33.5 (d, *C*-7), 28.0 and 27.4 [q, 3 C, $C(CH_3)_3$]; MS *m*/*z* 335 (M^+ − *t*-Bu, 2), 318 (0.4), 291 (3), 200 (15), 91 (100).

(1*R*,4*S*,6*S*,7*S*)-2-Oxa-5-azabicyclo[4.1.0]heptane-4,5,7-tricarboxylic acid 5-benzyl ester 7-ethyl ester 4-methyl ester (15a)

626 mg (2.24 mmol) of compound **(*S*)-5** were treated according to general procedure A using 4.5 equivalents of ethyl diazoacetate (6 h time of addition) to yield 512 mg (63%) of **15a**. (Found: C, 60.1; H, 5.11; N, 3.62. $C_{18}H_{21}NO_7$ requires C, 59.50; H, 5.83; N, 3.85%); $[\alpha]_D^{25}$ +5.5 (*c* 1.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3 : 2 mixture of rotamers α and β 7.35–7.28 (m, 5 H, *Ph*), 5.27 (AB, part A, $J = 12.5$ Hz, 0.6 H, CH_2Ph α), 5.22 (AB, part B, J = 12.5 Hz, 0.6 H, CH_2Ph α), 5.21 (AB, part A, $J = 13.1$ Hz, 0.4 H, CH_2Ph β), 5.13 (AB, part B, $J = 13.1$ Hz, 0.4 H, CH_2Ph β), 4.27 (d, $J = 3.2$ Hz, 0.6 H, *H*-4 α), 4.24 (d, $J = 3.2$ Hz, 0.4 H, *H*-4 β),

4.20–4.05 (m, 4 H, $CO_2CH_2CH_3$, *H*-3, and *H*-1), 3.84 (dd, J = 11.6, 3.6 Hz, 0.6 H, *H*-3 α), 3.80 (dd, J = 11.6, 3.6 Hz, 0.4 H, *H*-3 β), 3.74 (s, 1.8 H, CO_2CH_3 α), 3.63 (s, 1.2 H, CO_2CH_3 β), 3.53 (dd, J = 7.2, 3.6 Hz, 0.4 H, *H*-6 β), 3.49 (dd, J = 7.2, 3.6 Hz, 0.6 H, *H*-6 α), 2.38 (dd, J = 3.6, 2.4 Hz, 0.6 H, *H*-7 α), 2.29 (dd, J = 3.6, 2.4 Hz, 0.4 H, *H*-7 β), 1.26 (t, J = 7.2 Hz, 1 H, CO_2CH_3 β), 1.21 (t, J = 7.2 Hz, 2 H, CO_2CH_3 α); δ_C (50 MHz, $CDCl_3$) mixture of rotamers 170.5 and 170.0 (s, CO_2), 169.9 and 169.8 (s, CO_2), 156.1 and 155.4 (s, NCO_2), 135.8 and 135.5 (s, *i-Ph*), 128.2–127.2 (d, 5 C, *Ph*), 67.7 and 67.6 (t, CH_2Ph), 65.9 and 65.5 (t, *C*-3), 60.6 (t, $CO_2CH_2CH_3$), 58.1 and 57.8 (d, *C*-1), 55.4 and 54.9 (d, *C*-4), 52.6 (q, CO_2CH_3), 35.3 and 35.2 (d, *C*-6), 27.5 and 27.3 (d, *C*-7), 14.2 (q, $CO_2CH_2CH_3$); MS m/z 363 (M^+, 1.2), 246 (15.2), 228 (17.4), 91 (100).

(1*R*,4*S*,6*S*,7*S*)-2-Oxa-5-azabicyclo[4.1.0]heptane-4,5,7-tricarboxylic acid 5-benzyl ester 7-*t*-butyl ester 4-methyl ester (15b)

625 mg (2.24 mmol) of compound **(*S*)-5** were treated according to general procedure A using 4.5 equivalents of *t*-butyl diazoacetate (6 h time of addition) to yield 447 mg (51%) of **15b**. (Found: C, 61.36; H, 6.31; N, 3.46. $C_{20}H_{25}NO_7$ requires C, 61.37; H, 6.44; N, 3.58%); $[\alpha]_D^{26}$ +14.1 (*c* 0.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2 : 1 mixture of rotamers α and β 7.37–7.27 (m, 5 H, *Ph*), 5.30 (AB, part A, J = 13.1 Hz, 0.66 H, CH_2Ph α), 5.17 (AB, part B, J = 13.1 Hz, 0.66 H, CH_2Ph α), 5.22–5.12 (m, 0.66 H, CH_2Ph β), 4.25 (d, J = 2.8 Hz, 0.66 H, *H*-4 α), 4.23 (d, J = 2.8 Hz, 0.33 H, *H*-4 β), 4.13–4.06 (m, 0.66 H, *H*-1 β and *H*-3 β), 4.02 (dd, J = 7.2, 2.4 Hz, 0.66 H, *H*-1 α), 4.01 (d, J = 12.0 Hz, 0.66 H, *H*-3 α), 3.83 (dd, J = 12.0, 3.6 Hz, 1 H, *H*-3), 3.74 (s, 2 H, CO_2CH_3 α), 3.64 (s, 1 H, CO_2CH_3 β), 3.45 (dd, J = 7.2, 3.6 Hz, 0.33 H, *H*-6 β), 3.41 (dd, J = 7.2, 3.6 Hz, 0.66 H, *H*-6 α), 2.27 (dd, J = 3.6, 2.4 Hz, 0.66 H, *H*-7 α), 2.19 (dd, J = 3.6, 2.4 Hz, 0.33 H, *H*-7 β), 1.44 [s, 3 H, $CO_2C(CH_3)_3$ β], 1.37 [s, 6 H, $CO_2C(CH_3)_3$ α]; δ_C (50 MHz, $CDCl_3$) mixture of rotamers 170.1 (s, CO_2), 169.1 (s, CO_2), 156.2 (s, CO_2), 135.7 (s, *i-Ph*), 128.2–127.2 (d, 5 C, *Ph*), 80.9 [s, $C(CH_3)_3$], 67.7 (t, CH_2Ph), 65.9 and 65.4 (t, *C*-3), 57.6 (d, *C*-1), 54.9 (d, 2 C, *C*-4 and *C*-6) 52.5 (q, CO_2CH_3), 35.0 (d, *C*-7), 28.4 and 28.1 [q, 3 C, $C(CH_3)_3$]; MS (m/z) 335 (M^+ − *t*-Bu, 2), 318 (0.3), 291 (1), 200 (16), 91 (100).

(1*R*,4*R*,6*S*,7*S*)-2-Oxa-5-azabicyclo[4.1.0]heptane-4,5,7-tricarboxylic acid 5-benzyl ester 7-*t*-butyl ester 4-methyl ester (16)

390 mg (1.41 mmol) of compound **(*R*)-5** were treated according to general procedure A using 4.5 equivalents of *t*-butyl diazoacetate (6 h time of addition) to yield 336 mg (61%) of **16**, with identical NMR data as for **14b**. (Found: C, 61.11; H, 6.62; N, 3.54. $C_{20}H_{25}NO_7$ requires C, 61.37; H, 6.44; N, 3.58%); $[\alpha]_D^{25}$ +58.6 (*c* 1.0, $CHCl_3$).

(1*S*,4*R*,6*R*,7*R*)-2-Oxa-5-azabicyclo[4.1.0]heptane-4,5,7-tricarboxylic acid 5-benzyl ester 7-*t*-butyl ester 4-methyl ester (17)

Compound **17** was obtained from **(*R*)-5** as the minor diastereomer according to general procedure A, or in higher amounts according to general procedure B, with identical NMR data as for **15b**. (Found: C, 61.31; H, 6.34; N, 3.49. $C_{20}H_{25}NO_7$ requires C, 61.37; H, 6.44; N, 3.58%); $[\alpha]_D^{25}$ −15.8 (*c* 1.0, $CHCl_3$).

(1*R*,3*R*,4*S*,6*S*,7*S*)-3-Methyl-2-oxa-5-azabicyclo[4.1.0]heptane-4,5,7-tricarboxylic acid 5-benzyl ester 7-*t*-butyl ester 4-methyl ester (18)

To a solution of dihydroxazine **13** (450 mg, 1.54 mmol) in dry CH_2Cl_2 (4 mL) cooled in an ice–salt bath were added $Cu(OTf)_2$ (14 mg, 0.038 mmol), (*S*,*S*)-2,2′-isopropylidene-bis(4-*t*-butyl-2-oxazoline) (11 mg, 0.038 mmol) and phenylhydrazine (3.0 μL, 0.031 mmol). After 30 min, a 1.2 M solution of *t*-butyl-diazoacetate (5 eq.) in dry CH_2Cl_2 was added over 6 h. During the addition the volume was maintained constant, expelling CH_2Cl_2 by passing nitrogen through the flask. The reaction was then gently warmed to room temperature and stirred 16 h. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (hexanes–EtOAc 3 : 1) to yield 405 mg (65%) of **18**. (Found: C, 62.42; H, 6.93; N, 3.52. $C_{21}H_{27}NO_7$ requires C, 62.21; H, 6.71; N, 3.45%); $[\alpha]_D^{24}$ +34.6 (*c* 1.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3 : 1 mixture of rotamers α and β 7.34–7.24 (m, 5 H, Ph), 5.29 (AB, part A, J = 12.3 Hz, 0.75 H, CH_2Ph α), 5.21 (AB, part A, J = 12.2 Hz, 0.25 H, CH_2Ph β), 5.13 (AB, part B, J = 12.6 Hz, 0.75 H, CH_2Ph α), 5.06 (AB, part B, J = 12.3 Hz, 0.25 H, CH_2Ph β), 4.34 (q, J = 6.8 Hz, 0.75 H, *H*-2 α), 4.27 (q, J = 6.8 Hz, 0.25 H, *H*-2 β), 4.08 (s, 0.75 H, *H*-4 α), 4.03 (s, 0.25 H, *H*-4 α), 3.79 (dd, J = 7.2, 3.2 Hz, 0.25 H, *H*-1 β), 3.75 (dd, J = 7.2, 3.2 Hz, 0.75 H, *H*-1 α), 3.68 (s, 2.25 H, CO_2CH_3 α), 3.58 (s, 0.75 H, CO_2CH_3 β), 3.54 (dd, J = 7.2, 3.2 Hz, 0.25 H, *H*-6 β), 3.48 (dd, J = 7.2, 3.2 Hz, 0.75 H, *H*-6 α), 2.27 (t, J = 3.2 Hz, 0.75 H, *H*-7 α), 2.17 (t, J = 3.2 Hz, 0.25 H, *H*-7 β), 1.44 (d, J= 6.4 Hz, 2.25 H, $CHCH_3$ α), 1.44–1.41 (m, 0.75 H, $CHCH_3$ β), 1.41 [s, 2.25 H, $CO_2C(CH_3)_3$ β], 1.35 [s, 6.75 H, $CO_2C(CH_3)_3$ α]; δ_C (50 MHz, $CDCl_3$) mixture of rotamers 170.5 (s, CO_2), 169.4 (s, CO_2), 156.8 (s, NCO_2), 135.7 (s, *i-Ph*), 128.3–127.2 (d, 5 C, *Ph*), 80.7 [s, $C(CH_3)_3$], 70.1 and 69.6 (d, *C*-3), 67.6 (t, CH_2Ph), 58.8 and 58.4 (d, *C*-1), 52.7 (q, CO_2CH_3), 52.3 (d, *C*-4), 34.9 and 34.7 (d, *C*-6), 27.9 and 27.6 [q, 3 C, $C(CH_3)_3$], 27.5 (d, *C*-7), 17.8 (q, $CHCH_3$); MS m/z 405 (M^+, 0.1), 305 (2), 260 (9), 214 (51), 91 (100).

(1*R*,4*S*,6*S*,7*S*)-3-Methyl-2-oxa-5-azabicyclo[4.1.0]heptane-4,5,7-tricarboxylic acid 5-benzyl ester 4-methyl ester (19)

Compound **15b** (240 mg, 0.61 mmol) was dissolved in CH_2Cl_2 (2.8 mL) and TIS (125 μL, 0.61 mmol) and TFA (1.2 mL) were added sequentially. The mixture was stirred for 50 minutes at room temperature and then the solvents were removed under reduced pressure. The crude product obtained was redissolved in 5% Na_2CO_3 (20 mL) and the solution was extracted with Et_2O. The acqueous phase was acidified at pH 1–2 with concentrated HCl and extracted with CH_2Cl_2 (4 × 10 mL). The dichloromethane exctracts were combined, dried over Na_2SO_4 and concentrated under reduced pressure to obtain compound **19** (174 mg, 85%). (Found: C, 57.36; H, 5.21; H, 4.19. $C_{16}H_{17}NO_7$ requires C, 57.31; H, 5.11; N, 4.18%); $[\alpha]_D^{26}$ +5.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3 : 2 mixture of rotamers α and β 7.36–7.28 (m, 5 H, *Ph*), 5.27–5.10 (m, 2 H, CH_2Ph), 4.25 (d, J = 2.8 Hz, 0.6 H, *H*-4 α), 4.21 (d, J = 2.8 Hz, 0.4 H, *H*-4 β), 4.17–4.05 (m, 2 H, *H*-3), 3.85–3.78 (m, 1 H, *H*-1), 3.74 (s, 1.8 H, CO_2CH_3 α), 3.61 (s, 1.2 H, CO_2CH_3 β),

3.59–3.55 (m, 1 H, *H*-6), 2.39 (s, 0.6 H, *H*-7 α), 2.29 (s, 0.4 H, *H*-7 β); δ_C (50 MHz, $CDCl_3$) mixture of rotamers 175.6 and 175.0 (s, CO_2), 170.5 and 170.2 (s, CO_2), 156.3 and 155.8 (s, NCO_2), 135.8 and 135.4 (s, *i-Ph*), 128.4–127.3 (d, 5 C, *Ph*), 68.0 and 67.8 (t, CH_2Ph), 65.9 and 65.5 (t, *C*-3), 58.4 and 58.2 (d, *C*-4), 55.4 and 54.9 (d, *C*-1), 52.6 (q, CO_2CH_3), 36.0 and 35.8 (d, *C*-6), 27.4 (d, *C*-7); MS *m*/*z* 335 (M^+, 0.2), 290 (0.3), 246 (6), 232 (3), 200 (11), 91 (100).

(1*R*,4*S*,6*S*,7*R*)-7-Hydroxymethyl-3-methyl-2-oxa-5-azabicyclo[4.1.0]heptane-4,5-dicarboxylic acid 5-benzyl ester 4-methyl ester (20)

N-Methylmorpholine (52 μL, 0.47 mmol) and isobutyl chloroformiate (61 μL, 0.45 mmol) were added, at 0 °C, to a solution of compound **19** (144 mg, 0.43 mmol) in dry THF (4 mL). After 25 minutes, the white suspension was added dropwise at −78 °C to a suspension of $NaBH_4$ (32 mg, 0.86 mmol) in THF–MeOH 3 : 1 (4 mL). After 30 minutes at −78 °C a second portion of $NaBH_4$ (32 mg, 0.86 mmol) was added and the mixture was stirred for another 30 minutes at −78 °C and then was gently warmed to −40 °C, until all the mixed anhydride was consumed (TLC monitoring). The reaction was quenched with 10% AcOH–H_2O (2 mL), diluted with H_2O (8 mL), and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to a residue which was purified by flash column chromatography (EtOAc–hexanes 3 : 1, then EtOAc) to yield alcohol **20** (112 mg, 81%). (Found: C, 59.98; H, 5.71; N, 5.02. $C_{16}H_{19}NO_6$ requires C, 59.81; H, 5.96; N, 4.36%); $[a]_D^{25}$ +74.6 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1 : 1 mixture of rotamers α and β 7.40–7.29 (m, 5 H, Ph), 5.29–5.10 (m, 2 H, CH_2Ph), 4.16 (dd, *J* = 12.0, 3.2 Hz, 1 H, *H*-3), 4.03 (d, *J* = 12.0 Hz, 1 H, *H*-3), 3.83–3.72 (m, 2 H, CH_2OH), 3.74 (s, 1.5 H, CO_2CH_3 α), 3.64–3.59 (m, 1 H, *H*-4), 3.58 (s, 1.5 H, CO_2CH_3 β), 3.26–3.19 (m, 1 H, *H*-1), 2.76–2.70 (m, 1 H, *H*-6), 1.82–1.80 (m, 1 H, *H*-7); δ_C (50 MHz, $CDCl_3$) mixture of rotamers 170.8 and 170.5 (s, CO_2), 156.6 (s, NCO_2), 135.8 and 135.6 (s, *i-Ph*), 128.4–127.8 (d, 5 C, *Ph*), 67.8 (t, CH_2OH), 66.1 and 65.8 (t, CH_2Ph), 61.1 and 60.8 (t, *C*-3), 56.2 and 55.7 (d, *C*-1), 55.4 and 54.9 (d, *C*-4), 52.5 (q, CO_2CH_3), 30.3 and 30.0 (d, *C*-6), 28.6 and 28.2 (d, *C*-7); MS *m*/*z* 303 ($M^+ - OH$, 1), 290 (4), 218 (2), 200 (2), 91 (100).

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