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Stereoelectronic control of oxazolidine ring-opening: structural and chemical evidences☆

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Abstract—Ring opening of oxazolidines derived from tris(hydroxymethyl)aminomethane, L-serine and L-threonine was investigated. It was shown that $n(N)\rightarrow\sigma^*(C-O)$ electron delocalization (*endo*-anomeric effect) occurring in the five-membered ring plays a major role in the cleavage of the intracyclic C–O bond. The present work establishes that when the nitrogen lone pair is conjugated with a carbonyl group ($n(N)\rightarrow\pi(C{=}O)$ delocalization) as happens in *N*-acyloxazolidines, both hydrolysis and reductive ring-opening become much more difficult as a consequence of a concomitant decrease of oxygen basicity and of an increase of the intracyclic C–O bond strength.

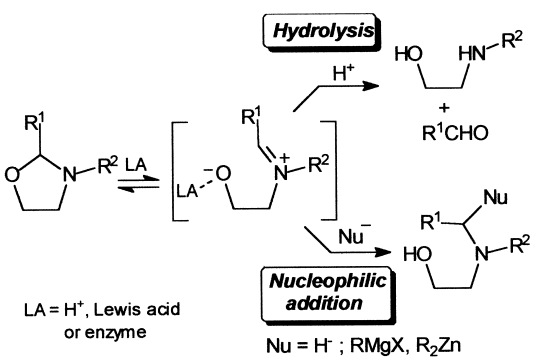
1. Introduction

Synthetic routes employing oxazolidines as cyclic protection of α-aminoalcohols have been widely used for the asymmetric synthesis of chiral amines, aminoalcohols and/or aminoacids.[1] Moreover, such derivatives were assumed to have potential as prodrug forms,[1a,b] as they undergo conversion to the parent compound. Indeed, oxazolidine derived from ephedrine has been proved to have sympathomimetic activity in several animal models.[2c] In both cases, the success of the approach relies on the cleavage of the 1,3-N,O ring.

The regioselectivity of oxazolidine ring-opening is long known to be governed by the higher stability of the acyclic iminium intermediate resulting from the C–O bond cleavage (see Scheme 1), compared with that of the oxocarbenium produced on C–N bond fission. Nevertheless, oxazolidine cleavage requires the presence of a Brönsted or a Lewis acid. For instance, nucleophilic Grignard[3] and dialkylzinc[4] additions are achieved in the presence of either a large excess of the organometallic reagent (5 equiv.) or a Lewis acid, e.g. $ZnCl_2$, $TiCl_4$, $BF_3{-}OEt_2$, MgX_2.

These observations indicate activation of the C–O bond through coordination of the Lewis acid to the oxygen, a situation which is commonly postulated for glycosides and related acetals reactions[5] and considered to be one of the consequence of the anomeric effect.[6,7]

Anomeric effect is due to a stereoelectronic preference for an antiperiplanar arrangement of a lone pair of electrons and an electron-acceptor bond that permits a no bond–double bond resonance effect.[8] Among other consequences, it is



Scheme 1.

☆ Part IV. For parts I–III, see Refs. 9–11.

Keywords: oxazolidines; crystal structure; ring-opening; stereoelectronic control.

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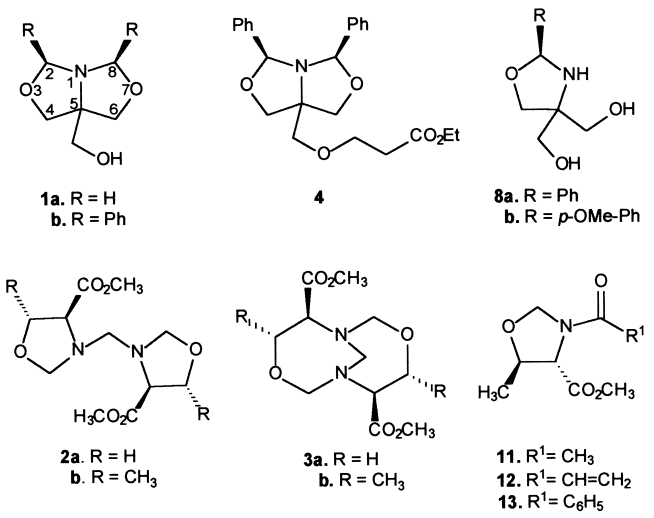
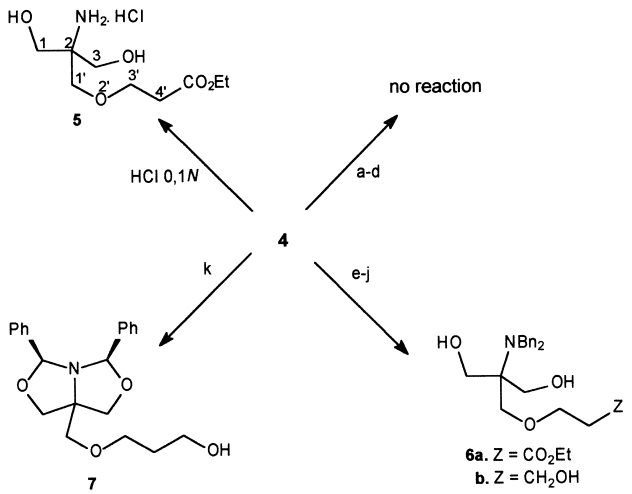


Scheme 2.

assumed that the heteroatom antiperiplanar to a doubly-occupied sp^3 orbital is made more basic because the resonance effect increases its electron density and consequently its affinity for a Lewis acid.

We recently obtained structural evidences for the manifestation of a strong anomeric effect occurring in the N–C–O fragment of 1,3-oxazolidines derived from tris(hydroxymethyl)aminomethane (TRIS®),[9] L-serine and L-threonine methyl ester.[10,11] Both ^1H and ^{13}C NMR spectroscopy as well as X-ray diffraction analyses proved unambiguously the existence of a $n(N)\rightarrow\sigma^*(C-O)$ electron delocalization characteristic of the anomeric effect. Such phenomenon was shown to control the conformational properties of the above derivatives both in the solid state and in solution.[10,11]

The work reported herein aims at establishing that the anomeric effect occurring in the oxazolidine derivatives reported in Scheme 2 governs also ring-opening.



Scheme 3.

Table 1. Procedures used to reduce compound **4**

Runs	Reactant	Solvent	*T* (°C)	Product	Yield (%)
a	$NaBH_4$	THF	20	No reaction	No reaction
b	$NaBH_4$	Ethanol	80	No reaction	No reaction
c	$NaBH_3CN$	THF	20	No reaction	No reaction
d	$NaBH_4$–AcOH	THF	20	No reaction	No reaction
e	$NaBH_4$–TFA	THF	20	**6a**	91
f	$NaBH_3CN$–TFA	THF	20	**6a**	86
g	$NaBH_4$–$AlCl_3$	THF	20	**6a**	89
h	$NaBH_3CN$–$AlCl_3$	THF	20	**6a**	88
i	BH_3	THF	20	**6a**	76
j	$LiAlH_4$–$AlCl_3$	THF	20	**6b**	80
k	$LiAlH_4$	THF	20	**7**	95

2. Results and discussion

2.1. Oxazolidines and bis(oxazolidines) derived from tris(hydroxymethyl)aminomethane

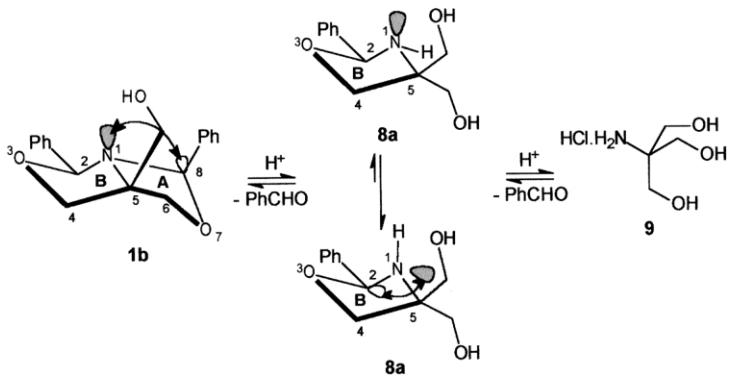
Compound **1b** was first converted into **4** by a Williamson addition[12] according to a solid–liquid phase transfer catalysis process.[13] Compound **4** was then submitted to various treatments summarized in Scheme 3 and Table 1 whose data call for the followings remarks:

1. Open-chain derivative **5** was readily obtained by smooth acid hydrolysis.
2. Using routine conditions, $NaBH_4$, $NaBH_3CN$ and $LiAlH_4$ proved unable to achieve ring-opening (runs a–d, k), even when $NaBH_4$ was previously treated with acetic acid[14,15] (run d). However, as expected, ethyl ester was easily reduced by $LiAlH_4$ (run k).
3. In contrast, the ester group was not affected whereas ring-opening occurred on treatment with an excess of both $NaBH_4$ and $NaBH_3CN$ previously treated with TFA (runs e, f) or used in the presence of $AlCl_3$ (runs g, h). A similar result was obtained by reacting **4** with BH_3 in THF (run i).
4. Concomitant ring-opening and ester reduction occurred when **4** was reacted with $LiAlH_4$ in the presence of $AlCl_3$ (run j).

It is worthwhile to note that reductive ring-opening is observed as soon as the reducing reagent is used in the presence of a Lewis acid ($AlCl_3$) or if the reducing reagent displays Lewis acid properties (BH_3). Most probably, the Lewis acid acts by coordinating the oxygen atom, which in turn weakens the C–O bond and therefore increases the rate of reduction. Boron and aluminum are known to have high affinity for oxygen as evident from the bond strengths in several molecules (metal-oxygen B–O=808 kJ/mol and Al–O=511 kJ/mol).[16] These values should be compared with those related to nitrogen atom: B–N=380 kJ/mol and Al–N=296 kJ/mol.

As mentioned above, ring-opening occurred also on treatment with $NaBH_4$ or $NaBH_3CN$ previously reacted with TFA. One can postulate that in such conditions, Lewis acid species are formed in situ according to one of the following equations. It is known that acyloxyborohydride derivatives are generated on reaction of metal hydrides with TFA:[17]

$$NaBH_4 + CF_3COOH \rightarrow CF_3COONa + H_2 + BH_3 \qquad (1)$$



Scheme 4.

$$Na(CF_3COO)_xBH_{4-x} + CF_3COOH \rightarrow CF_3COONa + H_2 + (CF_3COO)_xBH_{3-x} \quad (2)$$

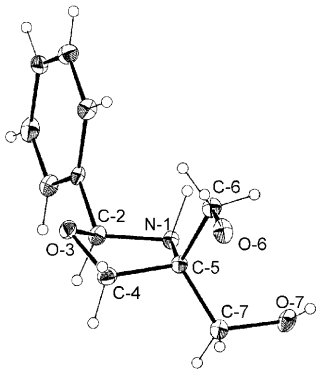
The fact that part of the reducing agent is consumed to generate Lewis acid species explains the necessity to use a large excess of metal hydride (2.5 molar equiv.) whereas reduction is completed with nearly stoechiometric amount of BH_3 in THF (1.1 molar equiv.).

In contrast to TFA, acetic acid is probably not strong enough to promote equilibria represented in Eqs. (1) and (2) to a sufficient extent. As a consequence, $NaBH_4/CH_3COOH$ (run d) is unable to achieve ring-opening. The present results corroborate previous observations[3,4] indicating that effective oxazolidine ring-opening requires the presence of an oxophilic catalyst (proton or Lewis acid).

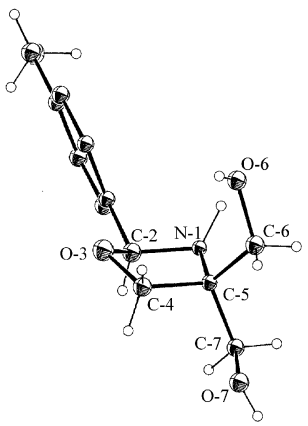
In compound **1b**, crystal data revealed the manifestation of a cooperative anomeric effect resulting from delocalization of electrons over the bond sequence O-3–C-2–N-1–C-8–O-7.[9] The conformation of ring A allowed $n(N) \rightarrow \sigma^*(C8–O7)$ electron interaction characteristic of a classical *endo*-anomeric effect (Scheme 4) whereas that of ring B allowed antiperiplanar interaction between the pseudo-equatorial sp^3 lone-pair on oxygen-3 with the C-2–N-1 antibonding orbital σ^*.[9] The reverse motion of electron in ring B is the result of N-1 becoming a much better electron acceptor than expected due to the *endo*-anomeric effect taking place in ring A. Electron delocalization mentioned above should influence the basicity of the oxygen atoms, as already observed for acetals,[5] thence their relative ease of protonation and/or coordination with a Lewis acid catalyst. Consequently, the ability of the C-8–O-7 bond to cleave should be enhanced whereas that of C-2–O-3 should be reduced.

Hydrolysis of compound **1b** was performed using various reagents, stoichiometries, temperatures and reaction times. None of these experiments indicated that hydrolysis proceeded in two steps. No intermediate oxazolidine was detected in the reaction mixture. Whatever the experimental conditions, the latter was shown to contain only the final product **9** or a mixture of compounds **1b** and **9**. This observation seemed to indicate that either there was no difference of reactivity between rings A and B or, because of nitrogen inversion, the conformation of the intermediate oxazolidine allowed antiperiplanar configuration of the nitrogen lone pair and of the C-2–O-3 acceptor bond (see the ORTEP representation reported in Fig. 1(a)); such arrangement is suitable to the manifestation of an *endo*-anomeric effect along the N-1–C-2–O-3 bond sequence. This hypothesis was unambiguously confirmed by X-ray diffraction analysis of oxazolidines **8a** and **8b**.

The three-dimensional structure of compound **8a** (Fig. 1(a)) clearly shows the ^{O}E envelope conformation adopted by the oxazolidine ring. Careful examination of crystal data

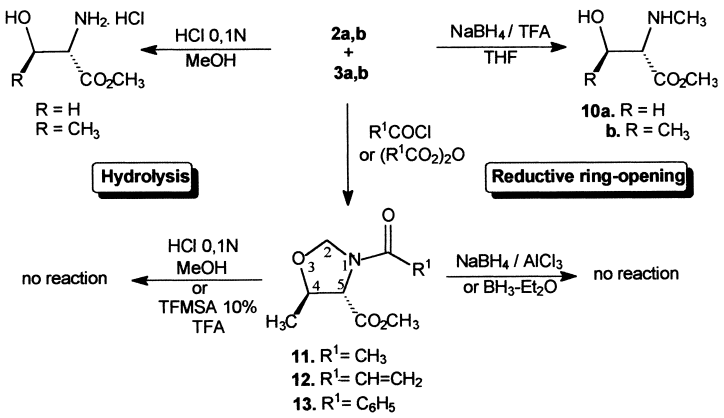


(a)



(b)

Figure 1. ORTEP views of compounds **8a** (a) and **8b** (b).



Scheme 5.

reveals that O-3 is 0.584 Å out of the plane C-2, N-1, C-5, C-4 (P1) whereas the latter makes a 40°8 dihedral angle with the envelope tip. More importantly, the pseudo-equatorial lone pair of electron on N-1 is almost antiperiplanar to the C-2–O-3 bond allowing $n(N) \rightarrow \sigma^*(C2-O3)$ electron delocalization. Indeed, the manifestation of the anomeric effect is corroborated by the contraction of the C2–N1 bond (1478 Å versus 1492 Å for the N1–C5 reference bond). Consequently, once ring A is opened, the basicity of O-3 becomes similar to that of O-8 as does the reactivity of rings A and B. A similar situation is observed for the *p*-methoxyphenyl analog **8b** (Fig. 1(b)).

2.2. *N*-Acyloxazolidines derived from L-threonine

One may expect electron-withdrawing and electron-donating groups attached to the nitrogen atom to affect the reactivity of the five-membered ring. In order to assess the possible influence of electronic and/or steroelectronic effects on the behavior of oxazolidines, various *N*-alkyl and *N*-acyloxazolidines derived from L-threonine were prepared from cycloadducts **2a**,**b** (**3a**,**b**)[18] (see Scheme 5).

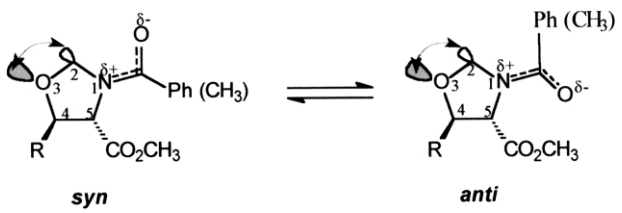
2.2.1. Synthesis. Compounds **11**–**13** were readily obtained by treatment of cycloadducts **2b** with the appropriate acyl chlorides or anhydrides derivatives at room temperature in a 1:1 water/acetonitrile mixture.

The following spectroscopic features are worth to mention: (i) in the mass spectra, the molecular ion peak is always accompanied by that of the acylium ion as well as by the residual fragment resulting from the cleavage of the amide bond (ii) all proton NMR signals were found significantly downfield compared with the equivalent signals in *N*-alkyl derivatives **2a**,**b** (**3a**,**b**) (iii) ^1H and ^{13}C NMR signals were duplicated indicating that, in $CDCl_3$ (or deuterio-benzene and acetone), these molecules existed as an unequal mixture of *cis* (*syn*)- and *trans* (*anti*)-rotational isomers (see Scheme 6), as commonly reported in similar situations[18–20] (iv) signals coalescence was observed when the temperature of the deuteriochloroform solution of **12** for instance, was increased to 42°C. The above observations unquestionably reflect delocalization of the nitrogen lone pair along the N-1–CO-Ph (CH_3) bond sequence.

2.2.2. Crystal structure of compound 13, stereoelectronic effects. Crystal data for compound **13** are presented in Section 4. X-Ray structure and atoms labeling are shown in Fig. 2. Estimated standard deviations (e.s.d.s.) for bond lengths and bond angles are ≤0.003 Å and ≤0.2°, respectively.

The main features of the three-dimensional structure of **13** may be summarized as follows:

1. The five-membered ring displays an ^{O}E envelope conformation in which O-3 is 0.624 Å out of P1 plane defined by atoms C-2, N-1, C-5, C-4 (rms deviation of fitted atoms, 0.031 Å). The dihedral angle between P1 and the envelope tip (plane C-2, O-3, C-4) is equal to 43°7.
2. Atoms C-2, N-1, C-5, C-10 can be considered as coplanar (average deviation from mean plane: 0.004 Å). That nitrogen atom has gained a marked sp^2 character is corroborated by the sum of bond angles around N-1



Scheme 6.

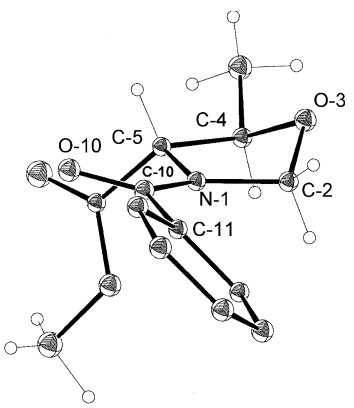


Figure 2. ORTEP views of compound **13**.

(358°5) as well as by a substantial decrease of the N-1–C-10 bond length: 1.348 Å compared with 1.469 Å for N-1–C-2.

3. In terms of stereoelectronic effect, these data confirm that electron delocalization of the lone pair of electron on nitrogen occurs essentially towards the carbonyl acceptor bond (n(N)→π(C=O) conjugation) to the detriment of the *endo*-anomeric effect (n(N)→σ*(C–O)) previously observed in NH and *N*-alkyloxazolidines.[9–11]
4. N-1 becoming more electropositive, electron delocalization of the sp^3 orbital on the ring oxygen into the σ* antibonding orbital of the C-2–N-1 acceptor bond takes place as illustrated in Scheme 6. The anomeric effect occurs now in the opposite direction as a result of the polar C–NCOR receiving electrons from the oxygen atom. Confirmation of such behavior arises from the observation that C-2–O-3 bond (1.412 Å) is noticeably shorter (≈0.03 Å i.e. 10×e.s.d.) than the O-3–C-4 reference bond (1.441 Å). Therefore, O-3–C-2 bond is strengthened while the basicity of the intracyclic oxygen is reduced.
5. For all these reasons, we predicted ring opening to be much more difficult in *N*-acyloxazolidines than in their *N*–H and *N*-alkyl counterparts.

Indeed, acid treatment of derivatives **11**–**13** according to the experimental conditions used for compounds **2** (**3**) proved unable to achieve ring-opening. Even the mixture TFMSA–10%/TFA reported in the literature[21] as being an efficient mean to hydrolyse oxaproline moieties of pseudo-peptide sequences was unsuccessful.

When experimental conditions used in run g (Table 1) were applied to compound **13** during 5 days, no ring-opening occurred. Treatment of the reaction mixture followed by column chromatography allowed to recover the unchanged starting material. Similarly, when **13** was treated according to the procedure employed in run i (24 h, 30°C, 2.4-fold excess of BH_3 in THF), no open-chain derivative was obtained.

All these observations supported the hypothesis that reactivity of the oxazolidine ring is dramatically reduced following amidification.

3. Conclusion

We have unambiguously established the crucial contribution of the anomeric effect to both the structure and reactivity of 1,3-oxazolidines. Indeed, C–O bond cleavage is greatly facilitated when n(N)→σ*(C–O) electron delocalization (*endo*-anomeric effect) is possible, i.e. when the lone pair of electron on the nitrogen atom is antiperiplanar to the C–O acceptor bond. The intracyclic oxygen becoming more basic, its interaction with the Lewis acid is greatly enhanced and ring-opening made easy. However, whenever the lone pair of electron of the donor is not available, anomeric effect does not occur and ring-opening becomes considerably more difficult.

4. Experimental

4.1. General

The progress of reactions and the homogeneity of compounds were monitored by thin layer chromatography (TLC Merck 254). Detection was achieved by exposure to UV light (254 nm) or by spraying a 1% potassium permanganate aqueous solution or 5% ninhydrin ethanolic solution and heating at 150°C. Column chromatography was performed on silica gel Si 60 (40–63 μm, Merck). Melting points were measured on a Büchi 530 apparatus and are reported uncorrected. The ^{1}H and ^{13}C-NMR spectra were recorded at 200, 250 or 400 MHz on a Bruker apparatus; atoms numbering is reported in Schemes 2 and 3, and Figs. 1 and 2. Chemicals shifts are given in ppm relative to tetramethylsilane using the deuterium signal of the solvent as a heteronuclear reference for ^{1}H and ^{13}C. Coupling constants are given in Hz. For rotational isomers, only characteristic peaks are listed. Elemental analysis were performed by the Service Central de Microanalyse du CNRS at Vernaison (France).

4.1.1. 5-Hydroxymethyl-1-aza-3,7-dioxabicyclo[3.3.0]-octane (1a). Tris(hydroxymethyl)aminomethane (TRIS) (2.00 g, 16.5 mmol) and paraformaldehyde (1.50 g, 50 mmol) were stirred at 65°C in anhyd. toluene (50 mL) until the reaction mixture becomes clear. The solvent was evaporated to dryness and the crude residue dissolved in diethylether (50 mL). The etheral solution was washed with a saturated Na_2CO_3 solution (10 mL). The aqueous phase was extracted with diethylether (3×50 mL) and the combined organic phase was dried over anhyd. Na_2SO_4 then evaporated to a white powder. The latter was column chromatographed (ethyl acetate) to afford colorless crystals (1.10 g, 45%, mp 60°C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.35 (1H, t, OH, J=6.2 Hz); 3.60 (2H, d, 2*H*-9, J=6.2 Hz); 3.78 and 3.84 (4H, AB syst., 2*H*-4, 2*H*-6, J_{gem}=8.8 Hz); 4.46 and 4.54 (4H, AB syst., 2*H*-2, 2*H*-8, J_{gem}=5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 64.44 (C-9); 73.45 (C-4, C-6); 74.10 (C-5); 88.44 (C-2, C-8); FAB$^+$ MS (GT) *m/z*: 146 $[M+H]^+$; 114 $[M+H-CH_3OH]^+$; Anal. calcd for $C_6H_{11}NO_3$: C, 49.65; H, 7.58; N, 9.65; O, 34.20; Found: C, 49.08; H, 7.64; N, 9.51; O, 34.29.

4.2. Hydrolysis—general procedure

A suspension of compound **1** or **4** (1 mmol) in a 0.1N methanolic solution of hydrochloric acid (20 mL) was heated for 1 h. After cooling, 20 mL of toluene was added to the reaction mixture which was then concentrated. The aqueous phase was extracted with diethylether (3×5 mL) and subjected to freeze drying.

4.2.1. 2-Amino-2-(4′-ethyloxycarbonyl-2′-oxabutyl)propane-1,3-diol hydrochloride (5). The title compound was obtained as an oily material (90%). ^{1}H NMR (250 MHz, D_2O) δ: 1.35 (3H, t, CH_3CH_2O, J=7.1 Hz); 2.77 (2H, t, 2H-4′, J=5.9 Hz); 3.73 (2H, s, 2H-1′); 3.81 (4H, s, 2H-1, 2H-3); 3.89 (2H, t, 2H-3′, J=5.9 Hz); 4.28 (2H, q, CH_3CH_2O, J=7.1 Hz); NMR ^{13}C (100 MHz, D_2O) δ: 13.64 (CH_3CH_2O); 34.94 (C-2); 61.07 (CH_3-CH_2O); 59.68 and 59.90 (C-1, C-3); 62.27, 67.24 and 68.34 (C-4,

C-1′, C-3′); 175.01 (C=O); FAB$^+$ MS (NBA) *m/z*: 222 [M+H]$^+$; 244 [M+Na]$^+$.

4.2.2. Tris(hydroxymethyl)aminomethane hydrochloride (9). The title compound was obtained as an oily material (80%). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 3.81 (6H, s, 2*H*-2, 2*H*-3, 2*H*-4); 4.92 (1H, s, OH); FAB$^+$ MS (GT) *m/z*: 122 [M+H]$^+$; 144 [M+Na]$^+$; 105 [M+H−(H_2O)]$^+$.

4.3. Reductive opening—2-(*N*,*N*′-dibenzyl)amino-2-(4′-ethyloxycarbonyl-2′-oxabutyl)propane-1,3-diol (6a)

Runs e–h (see Table 1). Trifluoroacetic acid or aluminium trichloride (5 mmol) was added dropwise or portionwise respectively to a suspension of the metal hydride (5 mmol) in anhyd. THF (5 mL) at 0°C. A solution of compound **4** (1.0 mmol) in anhyd. THF (5 mL) was added dropwise to the cooled mixture. After stirring 1 h at room temperature, the mixture was cooled and decomposed cautiously by 10% sodium hydroxide aqueous solution. The mixture was then concentrated and extracted with ethyl acetate (3×25 mL). The combined organic layer was dried over anhyd. Na_2SO_4 and evaporated to dryness. The oily residue was column chromatographed (petroleum ether/ethyl acetate 30:70, v/v) to afford a white solid (82–91%, mp 49°C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.28 (3H, t, C*H*$_3$CH$_2$O, *J*=7.1 Hz); 2.60 (2H, t, 2H-4′, *J*=5.8 Hz); 2.84 (2H, s, 2OH); 3.65 (2H, s, 2H-1′); 3.66 (2H, t, 2H-3′, *J*=5.8 Hz); 3.64 and 3.79 (4H, AB syst., 2H-1, 2H-3, J_{gem}=11.5 Hz); 3.96 (4H, s, 2×C*H*$_2$Ph); 4.20 (2H, q, 2H-CH$_3$C*H*$_2$O, *J*=7.1 Hz); 7.10–7.30 (10H, m, H-ar); FAB$^+$ MS (NBA) *m/z*: 402 [M+H]$^+$; 424 [M+Na]$^+$; 370 [M+H−CH_3OH]$^+$; 270 [M+H−CH_3O–CH_2–CH_2CO_2Et]$^+$; 91 [$PhCH_2$]$^+$; Anal. calcd for $C_{23}H_{31}NO_5$: C, 68.82; H, 7.73; N, 3.49; O, 19.95; Found: C, 68.48; H, 7.64; N, 3.57; O, 20.17.

Run i (BH_3–THF). A solution of compound **4** (1 mmol) in anhyd. THF (5 mL) was added dropwise to a cooled commercial solution of 1 M BH_3 in THF (1.1 molar equiv.). The reaction mixture was treated as reported above to afford the title compound (76%, mp 49°C).

4.3.1. 2-(*N*,*N*′-Dibenzyl)amino-2-(5′-hydroxy-2′-oxapentyl)propane-1,3-diol (6b). Aluminum trichloride (0.84 g, 6.3 mmol) was added portionwise to a suspension of lithium–aluminium hydride (0.25 g, 6.3 mmol) in anhyd. THF (5 mL). A solution of compound **4** (0.50 g, 1.3 mmol) in anhyd. THF (5 mL) was added dropwise to the cooled supension. After stirring 1 h at room temperature, the mixture was cooled and decomposed cautiously by 10% sodium hydroxide aqueous solution. The mixture was concentrated and extracted with ethyl acetate (3×10 mL). The combined organic layer was dried over anhyd. Na_2SO_4 and evaporated to dryness to give a colorless oil (0.36 g, 80%). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.90 (2H, m, 2H-4′); 2.51 (1H, br., C-5′–OH); 3.10 (2H, br., C-1–OH, C-3–OH); 3.56 (2H, t, 2H-5′, *J*=5.8 Hz); 3.62 (2H, s, 2H-1′); 3.80 (6H, m, 2H-1, 2H-3, 2H-3′); 3.96 (4H, s, 2×C*H*$_2$Ph); 7.10–7.20 (10H, m, H-ar); FAB$^+$ MS (NBA) *m/z*: 360 [M+H]$^+$; 382 [M+Na]$^+$; 328 [M+H−CH_3OH]$^+$; 91 [$PhCH_2$]$^+$. Anal. calcd for $C_{21}H_{29}NO_4$: C, 70.19; H, 8.07; N, 3.90; O, 17.82; Found: C, 70.48; H, 8.37; N, 3.77; O, 18.02.

4.3.2. 5-(5′-Hydroxy-2′-oxapentyl)-*cis*-2,8-diphenyl-1-aza-3,7-dioxabicylo[3.3.0]octane (7). A solution of compound **4** (0.20 g, 0.5 mmol) in anhyd. THF (5 mL) was added dropwise to a cooled suspension of lithium–aluminium hydride (0.04 g, 1.0 mmol) in anhyd. THF (5 mL). After stirring 1 h at 0°C, the mixture was cooled and decomposed cautiously by 10% sodium hydroxide aqueous solution. The mixture was then diluted with diethylether (10 mL) and the solution washed with brine (3×5 mL). The aqueous layer was extracted with diethylether (3×10 mL). The combined organic layer was dried over anhyd. Na_2SO_4 and evaporated to dryness to afford a white solid (0.17 g, 95%, mp 66–68°C). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.74 (2H, m, 2H-4′); 1.86 (1H, s, OH); 3.40 (2H, s, 2H-1′); 3.52 (2H, t, 2H-3′, *J*=5.8 Hz); 3.67 (2H, t, 2H-5′, *J*=5.8 Hz); 3.86 and 4.03 (4H, AB, 2H-4, 2H-6, J_{gem}=8.9 Hz); 5.51 (2H, s, 1H-2, 1H-8); 7.30–7.60 (10H, m, H-ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 32.51 (C-4′); 62.12 and 71.40 (C-1′, C-3′); 73.88 (C-4, C-6); 76.12 (C-5); 97.50 (C-2, C-8); 127.56, 128.60, 128.88, 139.67 (C-ar); FAB$^+$ MS (NBA) *m/z*: 356 [M+H]$^+$; 378 [M+Na]$^+$; 266 [M+H−$CH_3OCH_2CH_2CH_2OH$]$^+$; Anal. calcd for $C_{21}H_{25}NO_4$: C, 70.98, H, 7.04, N, 3.94; Found: C, 69.27; H, 7.04; N, 3.68.

4.4. Synthesis of compounds 8a,b—general procedure

TRIS (82.5 mmol) and benzaldehyde (or *p*-anisaldehyde) (82.5 mmol) were poured into a 250 mL round flask containing 150 mL of hot (80–100°C) toluene, fitted with a Dean and Stark apparatus. The mixture was refluxed until the expected amount of water was recovered in the graduated tube (4–5 h). The solvent was removed under reduced pressure, the residue dissolved in ethyl acetate (200 mL) followed by filtration to remove the unreacted material (Tris). The filtrate was evaporated to dryness and the solid residue purified by recrystallization from ethyl acetate. Pure title compounds were obtained as colorless crystals.

4.4.1. 5,5-Dihydroxymethyl-2-phenyl-1,3-oxazolidine (8a). 86%, Mp 64–65°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.10 (3H, br., NH, 2×OH); 3.20 and 3.65 (4H, AB syst., 2H-6, J_{gem}=11.2 Hz); 3.58 and 3.74 (4H, AB syst., 2H-6′, J_{gem}=10.8 Hz); 3.55 and 3.82 (2H, AB syst., 2H-4, J_{gem}=8.6 Hz); 5.45 (1H, s, H-2); 7.30–7.50 (5H, m, H-ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 64.70 and 65.23 (C-6, C-6′); 67.64 (C-4); 70.77 (C-5); 92.49 (C-2); 126.49, 129.03, 129.44, 139.06 (C-ar); FAB$^+$ MS (NBA) *m/z*: 210 [M+H]$^+$; 232 [M+Na]$^+$; 178 [M+H−(CH_3OH)]$^+$.

4.4.2. 5,5-Dihydroxymethyl-2-(4-methoxy)phenyl-1,3-oxazolidine (8b). 60%, Mp 114–115°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.10 (3H, br., NH, 2×OH); 3.60 and 3.75 (4H, AB syst., 2H-6, J_{gem}=1.2 Hz); 3.69 and 3.85 (4H, AB syst., 2H-6′, J_{gem}=10.7 Hz); 3.62 and 3.90 (2H, AB syst., 2H-4, J_{gem}=8.6 Hz); 3.84 (3H, s, OCH_3); 5.45 (1H, s, H-2); 7.10–7.40 (5H, m, H-ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.75 (OCH_3); 64.98 and 65.69 (C-6, C-6′); 67.56 (C-4); 70.72 (C-5); 92.30 (C-2); 114.37, 127.81, 131.28 (C-ar–H); 160.04 (C-ar–O); FAB$^+$ MS (NBA) *m/z*: 240 [M+H]$^+$; 208 [M+H−CH_3OH]$^+$; Anal. calcd for $C_{12}H_{17}NO_4$: C, 60.25; H, 7.11; N, 5.85; O, 26.72; Found: C, 60.48; H, 7.27; N, 5.77; O,26.98.

4.5. Reduction of compounds *2a*,b—general procedure

A solution of compound **2a** or **2b** (1.0 mmol) in anhyd. THF (5 mL) was added dropwise to a cooled suspension of sodium borohydride (0.38 g, 10.0 mmol) in anhyd. THF (5 mL). After stirring 5 h at room temperature, the mixture was cooled and cautiously decomposed with 10% NaOH aqueous solution. The mixture was concentrated and extracted with dichloromethane (3×20 mL). The combined organic layer was dried over anhyd. Na_2SO_4 and evaporated to dryness. The crude product was column chromatographed (diethylether/acetonirile/ ammonia 25%, 10:1:0.1, v/v) to afford colorless oils.

4.5.1. *N*-methyl-L-serine methyl ester (10a). 30%; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.43 (2H, br., NH, OH); 2.45 (3H, s, NCH_3); 3.40 (1H, m, H-2); 3.72 (2H, m, 2H-3); 3.75 (3H, s, OCH_3); FAB$^+$ MS (NBA) *m/z*: 134 $[M+H]^+$; 156 $[M+Na]^+$.

4.5.2. *N*-Methyl-L-threonine methyl ester (10b). 31%; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.22 (3H, d, NCH_3, J=6.4 Hz); 2.40 (3H, s, NCH_3); 2.60 (2H, br., NH, OH); 2.85 (1H, m, H-2); 3.70 (2H, m, 2H-3); 3.75 (3H, s, OCH_3); FAB$^+$ MS (NBA) *m/z*: 148 $[M+H]^+$; 116 $[M+H-CH_3OH]^+$.

4.6. General procedure for the *N*-acylation of compounds 2a,b

A solution of acyl chloride or acid anhydride (3 mmol) was added dropwise to a solution of compound **2a** or **2b** (1 mmol) in a 1:1 mixture of acetonitrile/saturated aqueous solution of Na_2CO_3 (10 mL). The pH was maintained above 7 by addition of solid Na_2CO_3. After stirring 16 h at room temperature, the mixture was concentrated, washed with a saturated NaCl aqueous solution and extracted with diethylether (3×30 mL). The combined organic layer was dried over anhyd. Na_2SO_4 and evaporated to dryness. The residue was column-chromatographed to afford *N*-acyl derivatives (**11**–**13**).

4.6.1. *N*-Acetyl-2(*S*)-ethyloxycarbonyl-3(*R*)-methyl-oxazolidine (11). Column chromatography (ethyl acetate) gave a colorless oil (70%). ^{1}H NMR (200 MHz, $CDCl_3$) δ (*syn* and *anti* rotational isomers): 1.46 and 1.48 (3H, 2d, CH_3C, J=6.1 Hz); 3.77 and 3.82 (3H, s, CH_3O); 4.00 and 4.11 (2H, 2d, H-5, J=6.5 Hz); 4.20 and 4.35 (1H, 2m, H-4); 4.87 and 5.38, 5.01 and 5.13 (2H, 2AB syst., 2H-2, J_{gem}=5.0 and 3.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: (*syn* and *anti* rotational isomers) 18.93 and 19.13 (CH_3); 22.55 and 25.59 (CH_3C=O); 53.02 and 53.37 (CH_3O); 63.38 and 64.74 (C-4); 79.01 and 79.45 (C-2); 79.50 and 80.11 (C-2); 167.34 and 168.85 (NC=O); 170.45 and 170.58 (OC=O); FAB$^+$ MS (NBA) *m/z*: 188 $[M+H]^+$; 210 $[M+Na]^+$; 146 $[M+H-CH_3CO]^+$; 43 $[CH_3CO]^+$; 375 $[2M+H]^+$; Anal. calcd for $C_8H_{13}NO_4$: C, 51.33; H, 6.95; N, 7.48; O,34.22; Found: C, 50.68; H, 7.27; N, 7.77; O, 34.07.

4.6.2. *N*-Acryloyl-2(*S*)-ethyloxycarbonyl-3(*R*)-methyl-oxazolidine (12). Column chromatography (petroleum ether/diethylether 80:20, v/v) gave a colorless oil (63%). ^{1}H NMR (250 MHz, $CDCl_3$) δ: (*syn* and *anti* rotational isomers) 1.48 (3H, d, CH_3, $J_{CH3,H-3}$=6.1 Hz); 3.79 (3H, s, OCH_3); 4.10–4.40 (2H, m, H-4, H-5); 4.85 and 5.45, 5.09 and 5.27 (2H, 2AB syst., 2H, 2H-2, J_{gem}=5.0 Hz and J_{gem}=3.7 Hz); 5.79 (1H, dd, CH_2=, J_{gem}=1.8 Hz, J_{cis}=10.2 Hz); 6.22 (1H, dd, CH_2=, J_{gem}=1.8 Hz, J_{tr}=16.8 Hz); 6.43 (1H, dd, CH=, J_{cis}=10.2 Hz, J_{tr}=16.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: (*syn* and *anti* rotational isomers) 18.84, 19.10 (CH_3); 53.08, 53.40 (CH_3O); 63.60, 64,.0 (C-4); 78.70, 79.12 (C-5); 79.60, 80,15 (C-2); 127.85, 128.01 (CH_2=); 129.90 (CH=); 163.10 (NC=O); 170.29, 170.85 (OC=O); FAB$^+$ MS (NBA) *m/z*: 200 $[M+H]^+$; 198 $[M-H]^+$; 222 $[M+Na]^+$; 55 $[CH_2=CHCO]^+$; 399 $[2M+H]^+$; Anal. calcd for $C_9H_{13}NO_4$: C, 54.27; H, 6.53; N, 7.03; O,32.16; Found: C, 54.68; H, 6.39; N, 7.17; O, 32.07.

4.6.3. *N*-Benzoyl-2(*S*)-ethyloxycarbonyl-3(*R*)-methyl-oxazolidine (13). Column chromatography (petroleum ether/diethylether 50:50, v/v) gave a solid material (60%) which recrystallized from diethylether to afford colorless crystals (mp 97–98°C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: (*syn* and *anti* rotational isomers) 1.54 (3H, d, CH_3); 3.83 (3H, s, CH_3O); 4.25 (1H, m, H-4); 4.42 and 5.03 (2H, br., 2H-2); 5.11 (1H, d, H-5, J=4.4 Hz); 7.40–7.60 (5H, m, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: (*syn* and *anti* rotational isomers) 15.65 and 18.89 (CH_3); 53.03 (CH_3O); 63.74 and 66.23 (C-3); 78.57 (C-2); 81.12 (C-5); 127.87, 128.94, 131.73, 135.21 (C-ar); 169.02 (NC=O); 170.42 (OC=O); FAB$^+$ MS (NBA) *m/z*: 250 $[M+H]^+$; 105 $[Ph-C=O]^+$; 272 $[M+Na]^+$; Anal. calcd for $C_9H_{15}NO_4$: C, 62.65; H, 6.02; N, 5.62; O,25.70; Found: C, 62.98; H, 6.09; N, 5.47; O, 25.97.

4.7. Supplementary material

Full crystallographic data (tables of crystallographic details, non-hydrogen coordinates, bond distances and bond angles, anisotropic thermal parameters, hydrogen coordinates and isotropic thermal parameters) have been deposited with the Cambridge Crystallographic Data Centre (CCDC no.188949, 188950 and 188951 for compounds **8a**, **8b** and **13**, respectively). This material is available on request from The Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (tel.: +44-1223-336408; fax: +44-1223-336033; e-mail deposit@ccdc.cam.ac.uk or http://www/ccdc.cam.ac.uk).

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18. In fact, the major compound obtained on condensation of L-serine methyl ester with formaldehyde was assigned the bicyclo[4.4.1]undecane structure (**3a**). The latter reacts similarly to its isomeric *N*,*N*′-methylenebis(oxazolidine) counter-part (see Ref. 10).
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