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Diastereoselective Aldol Condensation with 2-(β-Ethoxycarbonyl)oxazolidine Derived from Norephedrine. A Chiral Masked Synthon of Ethyl Formylacetate

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Abstract: Deprotonation of chiral masked synthetic equivalents of ethyl glyoxalate, derived from norephedrine, with a novel base formed by addition of *tert*-BuLi to *tert*-butyl formate, and subsequent reaction with aromatic aldehydes yields β-hydroxy esters in good yield and moderate to excellent diastereomeric excesses. Reductive transformation of the condensation products, and elimination of the chiral appendage leads to enantiomerically pure 2-aminomethyl-1,3-propanediol derivatives. © 1999 Elsevier Science Ltd. All rights reserved.

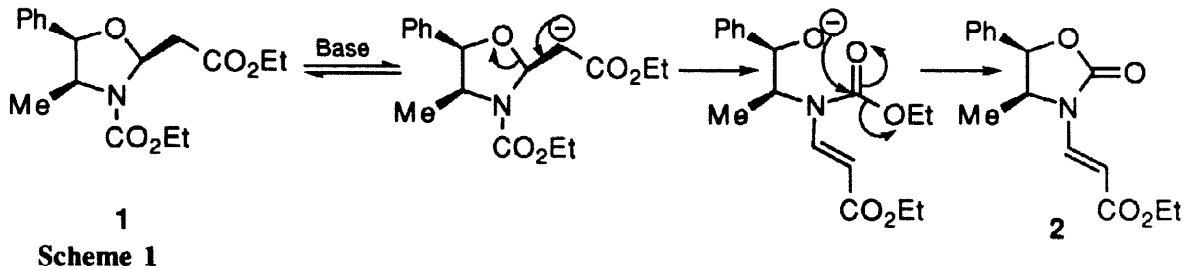
Keywords: Asymmetric synthesis; Chiral oxazolidines; Diastereoselectivity; Aldol reaction

Previously we have described[1] the preparation of chiral masked homoenolates and their transformation into enantiopure 3-substituted pyrrolidines. Upon transhalometallation, oxazolidines derived from 3-bromopropionaldehyde cyclize to lactams which, after deprotonation, react with aldehydes leading to chiral, non racemic, α-substituted lactams, easily transformed into enantiopure pyrrolidines.

Our interest in the formation of chiral nucleophiles[2] prompted us to study the preparation of a carbanion derived from 2-(β-ethoxycarbonyl)oxazolidine **1**, a chiral masked synthetic equivalent of a β-aldoester, and its application as a chiral nucleophile in diastereoselective additions to some aldehydes. Some previous reports on stereoselective α-alkylation of homologous γ-formyl esters, using oxazolidines as masked chiral equivalents of the aldehyde have been published.[3,4] The starting oxazolidine **1** was obtained in high yield (90%) and excellent diastereoselectivity (d.e. 92%) by transacetalization of ethyl 3,3-diethoxy propionate with (1R,2S)-ethoxycarbonyl norephedrine under kinetic conditions (BF_3, benzene, r.t., 30 min); the compound partially epimerizes at C-2 (75:25 mixture) after 4 hours of reaction.[5]

The first attempts to generate the enolate by treatment of **1** with different bases (LDA, t-BuOLi, Mg(N i-Pr2)2) in THF at -78°C were successful but it was not possible to trap the intermediate with electrophiles (D_2O, MeI, BnBr), and the oxazolidinone **2** was isolated quantitatively (Scheme 1).

This fact is easily understood as a fast elimination[6] on the initial carbanion, with concomitant ring



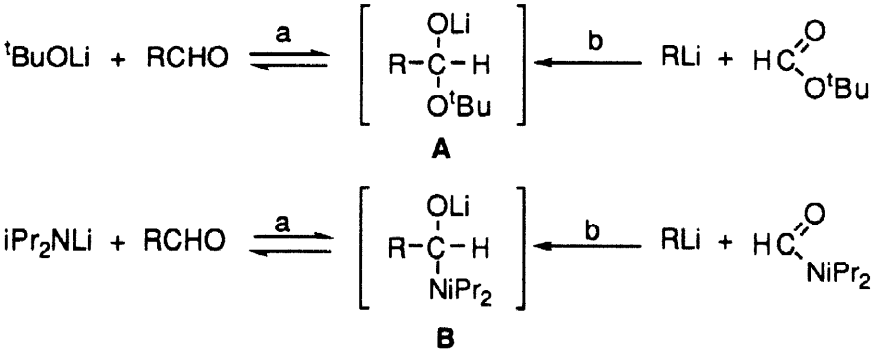
1 **2**

Scheme 1

PII: S0040-4020(99)00046-0

opening to the alkoxide, that immediately cyclizes to **2** by intramolecular substitution at the carbamate moiety. A similar cyclization, but on a cationic intermediate has been recently described for a related system.[7]

Trying to overcome this problem, we tested the conditions described by Seebach,[8] treating the oxazolidine **1** with a mixture of a non-enolizable aldehyde and lithium t-butoxide or lithium diisopropylamide. Using these conditions, it has been postulated that the formed intermediates **A** or **B** (Scheme 2, *via* a) act as a base and a source of electrophiles, increasing the ratio of condensation product. In our case, the reaction of **1** with **B** (LDA + C_6H_5CHO) leads to the oxazolidinone **2** quantitatively, whereas the condensation product **3** was isolated in very poor yields after reaction with **A** (^tBuOLi + C_6H_5CHO) depending on the reaction conditions (22% after 6 hours at 0°C, or 9% after 12 hours at 20°C). Under the first conditions, unchanged **1** (65%) was the major component of the reaction mixture while, with the second conditions, the elimination-cyclization product **2** (56%) was obtained predominantly.



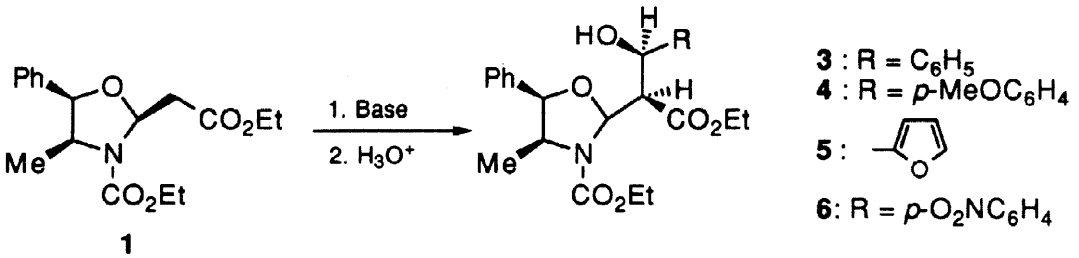
Scheme 2

Assuming that the intermediates **A** and **B** are responsible for simultaneous deprotonation and condensation processes,[8] and that the presence of an excess of base favoured the formation of **2**, we prepared these intermediates under non-equilibrium conditions by reaction of the corresponding alkyl lithiums with tert-butyl formate and diisopropyl formamide respectively (Scheme 2, *via* b). Some of the results obtained in the reaction of oxazolidine **1** with **A** or **B** prepared in this way are collected in Table 1.

The reaction does not work at low temperature, as shown by the fact that the starting oxazolidine **1** was recovered unchanged after stirring with 1.5 equivalents of the base for 4 hours at -10°C. Instead the transformation was completed in 30 min (entry 3) when the reaction was carried out at 20°C, although an increase of the reaction time decreases the yield of the condensation product **3** (compare entries 1 and 2 versus 3). In contrast, it was not possible to obtain the condensation product for aliphatic aldehydes (entries 11-14). Attempts to condense acetaldehyde lead to isolation of **2** (57-59%) and starting **1** (43-41%), whereas in the reaction with pivalaldehyde (entries 13-14) the oxazolidinone **2** was formed quantitatively. The best results using these experimental conditons were obtained (entry 6) when to the mixture of **1** and the base formed from PhLi and *tert*-butyl formate, at 20°C, one additional equivalent of benzaldehyde was added.

Taking into account these facts, a novel intermediate formed by reaction of ^tBuLi and *tert*-butyl formate was tested as a base (entries 7-10 in Table 1). To this end, 1.5 equivalents of the base, preformed by stirring *tert*-butyllithium and *tert*-butyl formate at -78°C, were added to a mixture of **1** (1 equiv.) and the corresponding aldehyde (1.5 equivalents) and the mixture was stirred at 20°C for 15 min. After the corresponding hydrolysis, the condensation products were isolated in moderate to good yields depending on the reactivity of the carbonyl

compound. The best yield was obtained for the most reactive *p*-nitrobenzaldehyde (entry 10) whereas anisaldehyde yielded **4** only in 56% yield.



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Scheme 3

Table 1. Condensation of Oxazolidine **1** with Aldehydes

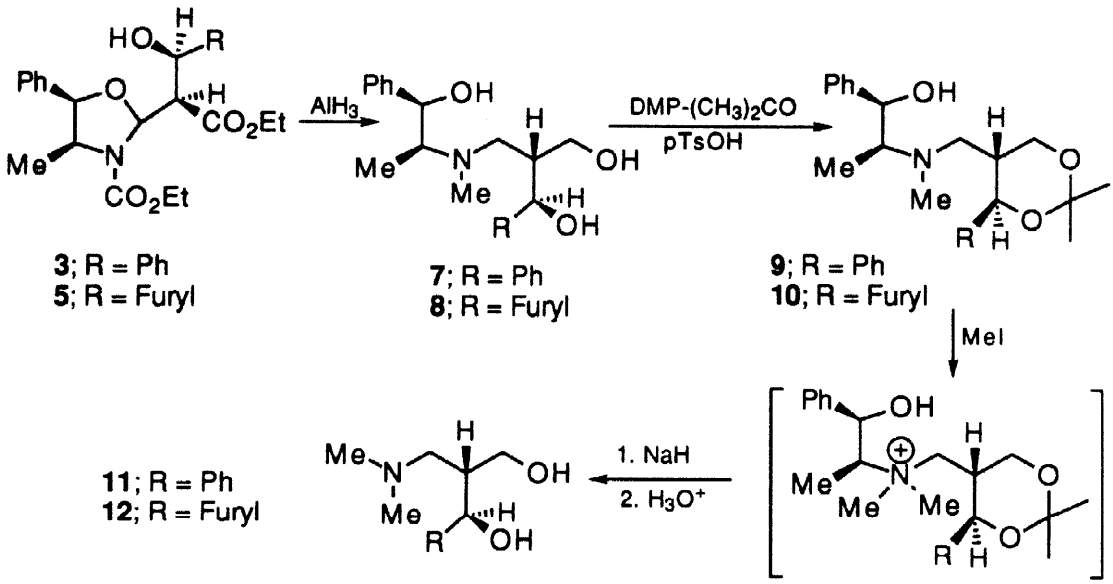
Entry	Base	R	t (min)	T(°C)	PRODUCTS (%) 1	2	3-6	d.e.[d]
1	PhLi+$HCO_2{}^tBu$	Ph	900	-78 to 20	(40)	(50)	**3**(10)	
2	PhLi+$HCO_2{}^tBu$	Ph	120	20	-	(79)	**3**(21)	
3	PhLi+$HCO_2{}^tBu$	Ph	30	20	-	(62)	**3**(38)	
4	PhLi+$HCO_2{}^tBu$	Ph	15	20	(21)	(58)	**3**(21)	
5	PhLi+$HCON(iPr)_2$	Ph	15	20	-	(68)	**3**(32)	
6	PhLi+$HCO_2{}^tBu$[a]	Ph	15	20	(14)	(24)	**3**(62)	
7	^{t}BuLi+$HCO_2{}^tBu$[b]	Ph	15	20	(11)	(20)	**3**(69)[63][c]	(>96)
8	^{t}BuLi+$HCO_2{}^tBu$[b]	4-$MeOC_6H_4$	15	20	-	(44)	**4**(56)	(56)
9	^{t}BuLi+$HCO_2{}^tBu$[b]	2-furyl	25	20	-	(31)	**5**(69)[51][c]	(81)
10	^{t}BuLi+$HCO_2{}^tBu$[b]	4-$NO_2C_6H_4$	15	20	-	(22)	**6**(78)	(-)[e]
11	MeLi+$HCO_2{}^tBu$	Me	15	20	(43)	(57)	-	
12	MeLi+$HCOH(iPr)_2$	Me	15	20	(41)	(59)	-	
13	^{t}BuLi+$HCO_2{}^tBu$	^{t}Bu	15	20	-	(100)	-	
14	^{t}BuLi+$HCON(iPr)_2$	^{t}Bu	15	20	-	(100)	-	

[a] One additional equivalent of PhCHO was added to the mixture of **1** and the base. [b] The base was added to a mixture of **1** and the corresponding aldehyde. [c] Numbers in square brackets correspond to the yields of the major diasteromers after purification. [d]Diastereomeric excesses were determined by integration of the ^{1}NMR signals of the reaction mixtures. [e]A mixture of the four possible diastereomers were detected

It is interesting to note the stereochemical outcome of the reaction. In the condensation of the enolate with aldehydes two new sterocenters are created. The most reactive p-nitrobenzaldehyde leads to a mixture of the four possible diastereomers, whereas only two diastereomers were detected for the reactions with p-anisaldehyde, although in modest d.e. (56%). The condensation with furfural yielded a mixture of two diastereoisomers in good d.e. (80%), and a single diastereoisomer was formed in the reaction with benzaldehyde (d.e. >96%).

The major diastereomers **3** and **5** were isolated pure by flash chromatography and transformed into 2-methylamino-1,3-propanediol derivatives **11** and **12** (Scheme 5). To this end, **3** and **5** were treated with an

excess of aluminium hydride[9] in THF at 0°C for 15 min leading to **7** (89%) and **8** (78%) respectively. These compounds were converted into the acetonides **9** and **10** by reaction with 2,2-dimethoxypropane and the relative stereochemistry at the dioxane moiety determined as trans by the coupling constant (J = 9.8 Hz) for protons H_4-H_5 and NOESY experiments.



Scheme 4

In addition, an X-ray diffraction experiment on compound **9** allowed the assignment of the absolute configuration as *4R,5R* in the 1,3-dioxane ring (Figure 1).

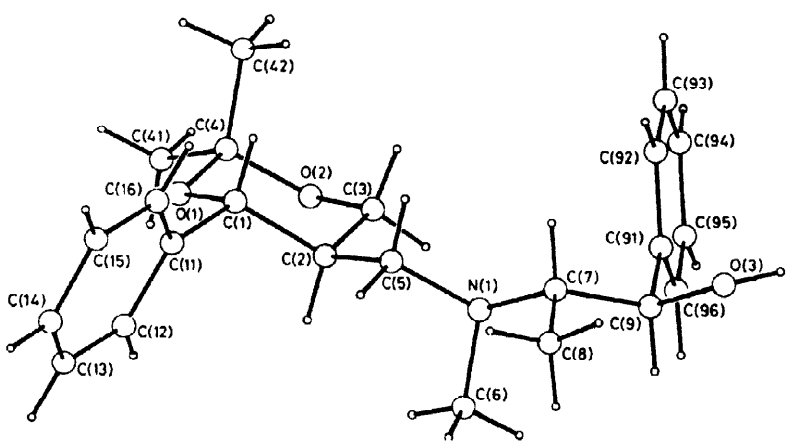
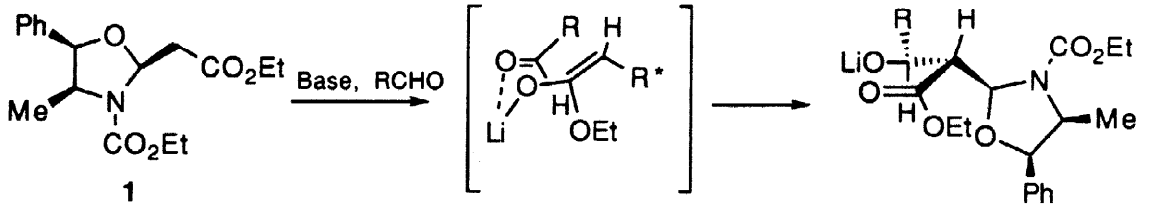


Figure 1. X-ray structure of compound **9**.

The elimination of the chiral appendage in **9** and **10** was carried out in two steps. Treatment of the acetonides with excess of methyl iodide leads to the quaternary salts,[11] that without isolation, were treated with sodium hydride yielding the enantiomerically pure (2R, 3R)-2-aminomethyl substituted 1,3-propanediols **11** and **12** in 62% and 96% respectively.

The stereochemistry of the two newly created stereocenters can be rationalized assuming a chair like transition state, where the *Z* enolate formed from the oxazolidines approaches to the carbonyl group in a *lk*[10] way, leading to the (R, R)-anti condensation products **3** and **5** as major or single diastereomers (Scheme 5).



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Scheme 5

Experimental

General. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded on Bruker AC300 or AMX300 spectrometers using TMS as internal standard. Mass spectra were registered on a Hewlett-Packard 5988-A mass spectrometer. IR spectra were recorded. as a thinfilm, on a Philips PU9706 spectrometer. Optical rotations were measured on a Perkin Elmer 241 Polarimeter in a 1 dm cell, and concentrations are given in g/100 ml. All reactions were carried out in anhydrous solvent under Argon atmosphere and in oven dried glassware. N-ethoxycarbonyl norephedrine **1** was obtained from (1R,2S)-norephedrine under Schotten-Baumann conditions. Ethyl 3,3-diethoxypropionate, commercially available, was distilled inmediately before use.

Crystal data for 9: $C_{23}H_{31}NO_3$, M_r = 369.49, hexagonal, space group P 6_3, a = 17.690 Å, c = 11.82(1) Å, V = 3204(3) Å^3, z = 6, D_x = 1.15 Mg m^{-3}, M_o Kα radiation (graphite crystal monochromator, λ = 0.71073 Å), μ = 0.75 cm^{-1}, F(000) = 1200, T = 293 K. Final conventional R = 0.043 (for 1734F_o>4 sigma(F_o)), and wR2 = 0.105 (for all reflections), w = 1.0/[sigma^2(F_o^2)+(0.053*P)^2] where P = (Max(F_o^2, 0)+2*F_c^2)/3. Total number of parameters 2454.

(2S,4S,5R)-N-Ethoxycarbonyl-2-(1'-ethoxycarbonylmethylen)-5-phenyl-4-methyl-1,3-oxazolidine (1). To a solution of (1R,2S)-N-ethoxycarbonyl norephedrine (2.23 g, 10 mmol) and ethyl 3,3-diethoxypropanoate (1.90 g, 10 mmol) in anhydrous benzene (100 mL) was added $BF_3.Et_2O$ (4.26 g, 30 mmol). The reaction mixture was stirred at room temperature until the reaction was finished (TLC). The mixture was neutralized with a saturated $NaHCO_3$ solution, extracted with EtOAc, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (silica gel, hexane/EtOAc 1/1) to give **1** (2.57 g, 80%) as a colorless oil. B.p. 210-212°C/0.9 Torr. $[\alpha]_D^{23}$ = -91.2 (c = 1.0, EtOH). IR (neat, cm^{-1}): 1730, 1690, 1600. MS (m/z, %): 321 (M^+, 0.07), 118 (100).^{1}H-NMR: 0.78 (d, 3H, J = 6.6 Hz), 1.30 (t, 6H, J = 7.1 Hz), 2.68 (dd, 1H, J_1 = 14.9 Hz, J_2 = 7.7 Hz), 3.00 - 3.32 (m, 1H), 4.17-4.24 (m, 5H), 5.12 (d, 1H, H-5, J = 5.6 Hz), 5.57 (dd, 1H, H-2, J_1 = 7.7 Hz, J_2 = 2.8 Hz), 7.28-7.34 (m, 5H).^{13}C-NMR: 14.1, 14.5, 16.1, 41.2, 55.6, 60.5, 61.2, 81.2, 85.6, 126.0, 127.7, 128.1, 135.8, 153.3, 169.6. [Found: C, 63.79; H, 7.02; N, 4.62. $C_{17}H_{23}NO_5$ requires C, 63.52; H, 7.22; N, 4.36].

Formation of lithium enolates and reaction with aldehydes.

Method A (entries 1-6 and 11-14 in Table 1). To a solution of *tert*-butyl formate or diisopropyl formamide (0.6 mmol) in dry THF (3 ml), under argon, at -78°C was added PhLi or the corresponding alkyllithium (0.6 mmol)

and the mixture stirred at that temperature for 15 min. The mixture was syringed to a solution of oxazolidine **1** (128.4 mg, 0.4 mmol) in THF (10 ml), and stirred at room temperature for the time indicated in Table 1. The reaction was quenched by addition of saturated NH_4Cl aqueous solution (5 mL) and extracted with CH_2Cl_2 (3x 20 mL). The organic layer was dried over anhydrous Na_2SO_4, the solvents were removed under reduced pressure and the residue was purified by flash chromatography(silica gel, CH_2Cl_2).

Method B (entries 7-10 in Table 1) To a solution of *tert*-butyl formate (0.6 mmol) in dry THF (3 ml) was added tBuLi (0.6 mmol), and the reaction mixture was stirred at -78°C for 15 min. This base was added to a solution of the oxazolidine **1** (128.4 mg, 0.4 mmol) and the corresponding aldehyde (0.4 mmol) in THF (10 ml) at room temperature. After 15-25 min, the reaction was hydrolized with a saturated aqueous solution of NH_4Cl, extracted with CH_2Cl_2 (3x 20mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the product was purified by flash chromatography (silica gel, CH_2Cl_2).

(4S,5R)-N-(2'-ethoxycarbonylethenyl)-5-phenyl-4-methyl-oxazolidinone (2). Colorless solid . M.p. 124-125°C (from hexane). $[\alpha]_D^{23}$ = +23.1 (c = 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3400, 1770, 1690, 1620. MS (m/z, %): 275 (M^+, 4), 231 (100). ^{1}H-NMR: 0.89 (d, 3H, J = 6.6 Hz), 1.30 (t, 3H, J = 7.1 Hz), 4.22 (q, 2H, J = 7.1 Hz), 4.38 - 4.42 (m, 1H), 5.27 (d, 1H, J = 14.4 Hz), 5.76 (d, 1H, J = 7.5 Hz), 7.27 - 7.44 (m, 5H), 7.93 (d, 1H, J = 14.4 Hz). ^{13}C-NMR: 13.1, 14.3, 54.4, 60.3, 79.4, 100.6, 125.7, 128.8 , 133.1, 137.3, 153.8, 166.6.[Found: C, 65.21; H, 6.40; N, 5.23. $C_{15}H_{17}NO_4$ requires C, 65.43; H, 6.23; N, 5.09].

(1'R,2'R,2S,4S,5R)-N-Ethoxycarbonyl-2(1'-ethoxycarbonyl-2'-phenyl-1-hydroxyethyl)-4-methyl-5-phenyl-1,3-oxazolidine (3). Colorless solid. M.p. 170-171°C (from CCl_4) . $[\alpha]_D^{23}$ = -107.3 (c = 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3400, 1730, 1680. MS (m/z, %): 428 (M^++1, 3), 206 (89), 107 (100). ^{1}H-NMR: 0.70 (d, 3H, J = 6.6 Hz), 1.21 (broad s, 1H), 1.28 (t, 6H, J = 7.1 Hz), 3.65 (dd, 1H, J_1 = 4.1Hz, J_2 = 3.7 Hz), 4.08-4.20 (m, 5H), 4.92-5.20 (m, 2H), 5.30 (d, 1H, J = 7.3 Hz), 7.26-7.46 (m, 10H).^{13}C-NMR: 13.9, 14.5, 15.9, 55.7, 56.4, 60.6, 61.5, 72.4, 81.1, 87.8, 125.70, 126.2, 126.6, 127.8, 128.2, 128.4, 135.7, 140.9, 154.3, 170.7. [Found: C, 67.30; H, 6.71; N, 3.40. $C_{24}H_{29}NO_6$ requires C, 67.43; H, 6.84; N, 3.28].

(1'R,2'R,2S,4S,5R)-N-Ethoxycarbonyl-2-(1'-ethoxycarbonyl-2'-hydroxy-2'-(4-methoxy phenyl)-ethyl)-4-methyl-5-phenyl-1,3-oxazolidine (4). Colorless oil. IR(neat, cm^{-1}): 3420, 1690. ^{1}H-NMR (Mixture of diastereomers): 0.69 (d, 3H, J = 6.7 Hz), 1.18-1.37 (m, 7H), 3.66 (dd, 1H, J_1 = 8.7 Hz, J_2 = 3.5 Hz), 3.79 (s, 3H), 4.03-4.27 (m, 6H), 4.95-5.09 (m, 1H), 5,27 (dd, 1H, J_1 = 8.7 Hz, J_2 = 4.0 Hz), 6.86-6.90 (m, 2H), 7.26-7.60 (m, 7H). ^{13}C-NMR (Mixture of diastereomers): 14.0, 14.5, 15.9, 55.2, 55.7, 56.3, 60.6, 61.5, 72.0, 81.2, 87.9, 113.8, 126.2, 127.8, 128.2, 132.9, 135.7, 159.3, 170.9.

(1'R,2'R,2S,4S,5R)-N-Ethoxycarbonyl-2-(1'-ethoxycarbonyl-2'-furyl-2'-hydroxyethyl)-4-methyl-5-phenyl-1,3-oxazolidine (5). Colorless oil. IR (neat, cm^{-1}): 3400, 1680. CIMS(m/z, %): 418 (M^++1, 1.5), 234 (100). ^{1}H-NMR: 0.61 (d, 3H, J = 6.7 Hz), 1.14 (t, 3H, J = 7.1 Hz), 1.22 (t, 3H, J = 6.9 Hz), 3.67-3.82 (m, 2H), 3.95-4.21 (m, 6H), 4.90 (d, 1H, J = 5.3 Hz), 5.22 (t, 1H, J = 7.4 Hz), 6.22-6.28 (m, 2H), 7.15-7.30 (m, 6H). ^{13}C-NMR: 13.8, 14.4, 15.8, 53.9, 55.6, 60.6, 61.5, 65.9, 81.1, 110.1, 126.1, 127.7, 128.1, 135.5, 142.2, 153.5, 154.1, 170.3. [Found: C, 63.47; H, 6.31; N, 3.54.$C_{22}H_{27}NO_7$ requires C, 63.28; H, 6.52; N, 3.36].

(1'R,2'R,2S,4S,5R)-N-Ethoxycarbonyl-2-(1'-ethoxycarbonyl-2'-hydroxy-2'-(4-nitro phenyl)-ethyl)-4-methyl-5-phenyl-1,3-oxazolidine (6). Colorless oil. IR(neat, cm^{-1}): 3420, 1700. ^{1}H-NMR (Mixture of diastereoisomers): 0.76 (d, 3H, J = 6.7 Hz), 1.05 (t, 1H, J = 9.2 Hz),1.09-1.14 (m,

3H), 1.30 (t, 3H, J = 7.1 Hz), 3.50-3.59 (m, 1H), 4.04-4.27 (m, 5H), 5.05-5.12 (m, 2H), 5,36-5.44 (m, 1H), 7.26-7.40 (m, 5H), 7.63 (d, 2H, J = 8.8 Hz), 8.2 (d, 2H, J = 8.8 Hz). ^{13}C-NMR (Mixture of diastereomers): 13.8, 14.3, 15.9, 55.6, 56.4 , 60.7, 61.6, 71.2, 81.2, 87.3, 123.3, 125.7, 126.0, 127.8,135.2, 147.2, 148.5, 154.5, 169.9.

Reduction of compounds **3** *and* **5** . To a suspension of $LiAlH_4$ (76 mg, 2 mmol) and $AlCl_3$ (75.0 mg, 0.4 mmol) in dry THF (5 mL) cooled to 0°C, was added slowly a solution of **3** or **5** (0.4 mmol) in THF (5 mL) and the mixture was stirred at that temperature for 15 min. The reaction was quenched with aqueous solution of NH_4Cl (3 mL), filtered and acidified with diluted HCl solution. The aqueous layer was extracted with CH_2Cl_2 (3x 20 ml), basified with NaOH solution and extracted with CH_2Cl_2 (3x 20 ml). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The products were purified by flash chromatography (silica gel, CH_2Cl_2/EtOAc: 1/1) to yield aminodiols **7** (111.8 mg, 85%) and **8** (102.1 mg, 80%).

(1R,2S,5R,6R)-3-Aza-1,6-diphenyl-5-hydroxymethyl-2.3-dimethyl-1,6-hexanediol (7). Colorless oil. $[\alpha]_D^{23}$ = -12.3 (c = 1.2, $CHCl_3$).IR neat, cm^{-1}): 3460. 1210, 955. ^{1}H-NMR: 0.97 (d, 3H, J = 6.7 Hz), 2.01-2.13 (m, 1H), 2.20 (s, 3H), 2.60-2.70 (m, 2H), 2.72-2.88 (m, 1H), 3.05-3.50 (broad s, 3H), 3.65-3.70 (m, 2H), 4.74 (d, 1H, J = 5.0 Hz), 4.79 (d, 1H, J = 4.7 Hz), 7.22-7.52 (m, 10H). ^{13}C-NMR: 8.8, 37.8, 43.6, 56.2, 62.7, 65.2, 74.7, 74.9, 125.9, 127.1, 127.2, 127.8, 127.9, 128.0, 128.1, 142.9, 143.2. [Found: C, 73.19; H, 8.41; N, 4.06.$C_{20}H_{27}NO_3$ requires C, 72.90; H, 8.27; N, 4.25].

(1R,2S,5R,6R)-3-Aza-1-phenyl-6-furyl-5-hydroxymethyl-2.3-dimethyl-1,6-hexanediol (8). Colorless oil. $[\alpha]_D^{23}$ = +10.2 (c = 1.7, $CHCl_3$). IR(neat, cm^{-1}): 3480, 1195. ^{1}H-NMR: 1.79 (d, 3H, J = 6.8 Hz), 2.20 (s, 3H), 2.21 - 2.28 (m, 1H), 2.56 - 2.65 (m, 2H), 2.78 - 2.86 (m, 1H), 3.44 - 3.59 (m, 2H), 4.55 (broad s, 3H), 4.65 (d, 1H, J = 5.4 Hz), 4.79 (d, 1H, J = 3.9 Hz), 6.16-6.26 (m, 2H), 7.14-7.28 (m, 6H). ^{13}C-NMR: 8.2, 37.6, 41.5, 55.7, 62.5, 65.2, 68.8, 74.1, 106.8, 110.0, 125.8, 127.0, 128.0, 128.1, 141.6, 142.7, 155.5. [Found: C, 67.87; H, 8.08; N, 4.56.$C_{18}H_{25}NO_4$ requires C, 67.67; H, 7.89; N, 4.39].

Preparation of acetonides **9** *and* **10**. To a solution of aminotriols (**7** or **8**) (0.4 mmol), in 2,2-dimethoxypropane (3 ml) and acetone (3 ml) was added a small amount of p-toluensulfonic acid. The reaction mixture was refluxed for 12 h. The reaction was cooled to room temperature, neutralized with K_2CO_3, filtered and the solvent was removed under reduced pressure. The acetals (**9** or **10**) were purified by flash chromatography (silica gel, CH_2Cl_2).

(4R,5R,3'S,4'R)-5-(2'-Aza-2',3'-dimethyl-4'-hydroxy-4'-phenyl-butyl)-2,2-dimethyl-4-phenyl-1,3-dioxane (9). Colorless solid. M.p. 155-156°C. (from hexane/EtOAc). $[\alpha]_D^{23}$ = -54.3 (c = 1.6, $CHCl_3$).IR(nujol, cm^{-1}): 3380, 1190. ^{1}H-NMR : 0.78 (d, 3H, J = 6.8 Hz), 1.46 (s, 3H), 1.52 (s, 3H), 1.95 (s, 3H), 2.09 - 2.32 (m, 3H), 2.55-2.60 (m, 1H), 2.61-2.70 (s br, 1H), 3.61 (dd, 1H, J = 11.9, 10.5 Hz), 3.91 (dd, 1H, J_1 = 11.9, J_2 = 4.5 Hz), 4.45 (d, 1H, J = 9.8 Hz), 4.62 (d, 1H, J = 4.8 Hz), 7.19-7.37 (m, 10H). ^{13}C-NMR: 10.0, 19.1, 29.7, 37.1, 39.1, 54.8, 63.9, 64.9, 73.4, 76.4, 98.7, 125.9, 127.0, 127.5, 128.0, 128.3, 128.5, 140.1, 142.5. [Found: C, 74.62; H, 8.58; N, 3.92. $C_{23}H_{31}NO_3$ requires C, 74.75; H, 8.46; N, 3.79].

(4R,5R,3'S,4'R)-5-(2'-Aza-2',3'-dimethyl-4'-hydroxy-4'-phenyl-butyl)-2,2-dimethyl-4-furyl-1,3-dioxane (10). Colorless oil. $[\alpha]_D^{23}$ = +42.2 (c = 2.2, $CHCl_3$). IR(neat, cm^{-1}): 3390, 1180, 960. ^{1}H-NMR : 0.85 (t, 3H, J = 6.9 Hz), 1.43 (s, 3H), 1.50 (s, 3H), 2.10 (s, 3H), 2.18-2.31 (m, 2H), 2.36-2.52 (m, 1H), 2.57-2.67 (m, 1H), 3.10 (broad s, 1H), 3.56 (dd, 1H, J_1 = 12.0, J_2 = 10.5 Hz), 3.91 (dd, 1H,

J_1 = 12.0, J_2 = 4.9 Hz), 4.57 (d, 1H, J = 10.5 Hz), 4.69 (d, 1H, J = 4.9 Hz), 6.32-6.37 (m, 2H), 7.21-7.43 (m, 6H). ^{13}C-NMR: 10.0 , 19.3 , 29.1 , 36.5, 37.8, 54.9 , 63.6 , 65.0, 69.1, 73.6, 98.8, 108.6, 110.1, 125.9, 128.1, 142.4, 152.9. [Found: C, 70.38; H, 7.91; N, 4.09. $C_{21}H_{29}NO_4$ requires C, 70.15; H, 8.14; N, 3.90].

Elimination of the chiral appendage. A solution of acetals (**9** or **10**) (0.4 mmol) in methyl iodide (4 ml) was stirred for 48 h at room temperature. The excess of methyl iodide was removed under vacuum, and the solid residue was suspended in anhydrous THF (10 mL) and treated with NaH (0.48 mmol). The mixture was refluxing for 3 h, cooled to r.t., quenched with water and acidified with a diluted HCl solution. The aqueous layer was extracted with CH_2Cl_2 (3x 20 ml), and then was treated with a diluted NaOH solution. This basic solution was extracted with CH_2Cl_2 (3x 20 ml), the organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated in vacuo. The residue was purified by flash chromatography (silicagel, CH_2Cl_2/EtOAc: 1/1).

(1R,2R)-2-(N,N-dimethylaminomethyl)-1-phenyl-1,3-propanediol (11). Colorless oil. $[\alpha]_D^{23}$ = -2.8 (c = 1.0, $CHCl_3$). IR (neat, cm^{-1}): 3350. CIMS (m/z, %): 210 (M^++1, 99.7), 238 (M^++29, 7), 250 (M^++41, 3.5), 137 (100). ^{1}H-NMR: 2.25 (s, 6H), 2.27-2.47 (m, 3H), 3.56-3.80 (m, 4H), 4.75 (d, 1H, J = 4.9 Hz), 7.24-7.38 (m, 5H). ^{13}C-NMR: 43.1, 45.7, 60.5, 64.0, 75.2, 126.3, 127.5, 128.3, 142.6. [Found: C, 68.64; H, 9.29; N, 6.94. $C_{12}H_{19}NO_2$ requires: C, 68.85; H, 9.16; N, 6.70].

(1R,2R)-2-(N,N-dimethylaminomethyl)-1-furyl-1,3-propanediol (12). Colorless solid. M.p. 91-93°C.(from hexanes) $[\alpha]_D^{23}$ = +3.75 (c = 0.5, EtOH). IR (neat, cm^{-1}): 3350. CIMS (m/z, %): 200 (M^++1,100), 228 (M^++29, 5). ^{1}H-NMR: 2.38 (s, 6H), 2.45 - 2.58 (m, 3H), 3.25 (broad s, 2H), 3.63 (dd, 2H, J_1 = 11.1 Hz, J_2 = 5.2 Hz), 4.88 (d, 1H, J = 4.8 Hz), 6.33-6.40 (m, 2H), 7.37-7.42 (m, 1H). ^{13}C-NMR: 41.5, 45.4, 59.6, 63.2, 69.5, 107.1, 110.2, 141.8, 155.6. [Found: C, 60.14; H, 8.46; N, 7.14. $C_{10}H_{17}NO_3$ requires: C, 60.26; H, 8.60; N, 7.03].

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