

Highly diastereoselective addition of nitromethane anion to chiral α -amidoalkylphenyl sulfones. Synthesis of optically active α -amino acid derivatives †

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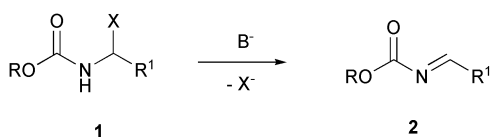
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Optically active *syn*- α -amidoalkylphenyl sulfones can be prepared from chiral aldehydes in anhydrous conditions using benzenesulfonic acid. These sulfones in basic conditions give *N*-acylimines that react with sodium methanenitronate to afford the corresponding nitro adducts with high *anti* diastereoselectivity. PM3 semiempirical calculations provide a rationale for the observed opposite stereoselectivity. The obtained nitro derivatives undergo a Nef reaction followed by a methylation giving optically active β -hydroxy- α -amino acid and α,β -diamino acid esters in good yield. These amino acid derivatives are important building blocks for the preparation of biologically active compounds.

Introduction

Imines and related derivatives occupy a central role as reactive substrates for the synthesis of functionalized amines.¹ Their importance parallels that of the carbonyl group for the preparation of hydroxy derivatives. Reactivity of imines strongly depends upon the nature of the substituent directly linked to the nitrogen atom. Imines bearing *N*-alkyl or *N*-aryl groups are easily prepared and stored but their reactivity towards nucleophilic reagents is not particularly prominent.² This lack of reactivity dictates the utilization of powerful carbanionic reagents that often promote enolisation rather than addition to imino derivatives. Electron withdrawing groups on nitrogen can suitably enhance the electrophilic character of carbon–nitrogen double bonds. Sulfonyl,³ sulfinyl,⁴ as well as other *N*-derivatives⁵ have been successfully used to promote nucleophilic additions in mild conditions. *N*-Acyl and *N*-carbamoyl imines, known as amidoalkylating agents,⁶ are also very active as electrophilic substrates but are too unstable to be stored when prepared from aliphatic aldehydes since they readily tautomerize to the corresponding enecarbamate.⁷ Indeed, *N*-acylimines **2** are usually generated *in situ* starting from *N*-acyl- α -substituted amines **1** by a base induced elimination (Scheme 1).⁸



Scheme 1

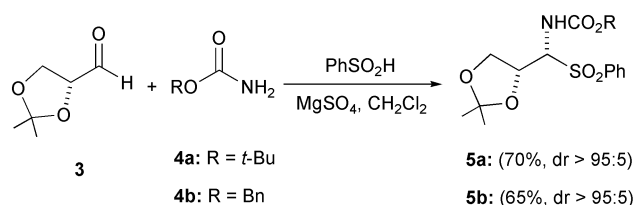
Among various derivatives of type **1**, α -amidoalkylphenyl sulfones (**1**, X = SO₂Ph) have recently emerged as profitable precursors of *N*-acylimines **2** in various reactions with nucleophilic reagents.⁹ These sulfonyl derivatives are usually prepared

by reaction of an amide or a carbamate with an appropriate aldehyde and sodium benzenesulfinate in the presence of formic acid.¹⁰ Since this reaction is carried out in water as solvent, the presence of acid-labile groups in the aldehyde are clearly incompatible with these conditions. However, we have recently demonstrated that α -amidoalkylphenyl sulfones can be prepared in anhydrous conditions using benzenesulfonic acid in dichloromethane without the need for other acid promoters.¹¹ In this paper we report the synthesis of optically active α -amidoalkylphenyl sulfones starting from chiral aldehydes and their utilization for the synthesis of α -amino acid derivatives in diastereomerically enriched form.

Results and discussion

Optically active sulfones from chiral α -alkoxy aldehydes

As a first attempt we used (*R*)-2,3-*O*-isopropylidene-glyceraldehyde **3**,¹² which features the presence of a ketal group, to obtain the corresponding sulfones (*R,R*)-**5** (Scheme 2).



Scheme 2

These sulfones were produced with high *syn* diastereoselectivity that has been evaluated by X-ray analysis on compound **5a** (Fig. 1).¹³ Following the general reactivity of derivatives **1**, sulfones **5** were expected to react with nucleophilic reagents in a diastereoselective fashion giving the corresponding adducts. Aza-Henry reaction of imines with nitronate anions provides a rapid entry to β -nitro enamines that are amenable to further synthetic transformations.¹⁴ Reaction of sulfones **5** with sodium methanenitronate at room temperature gave the corresponding nitro derivatives **6** in good yield (Scheme 3).¹⁵

† Electronic supplementary information (ESI) available: Computational results output for the calculated structures. Transition state models leading to compounds **21** and **22**. See <http://www.rsc.org/suppdata/ob/b3/b309211a/>

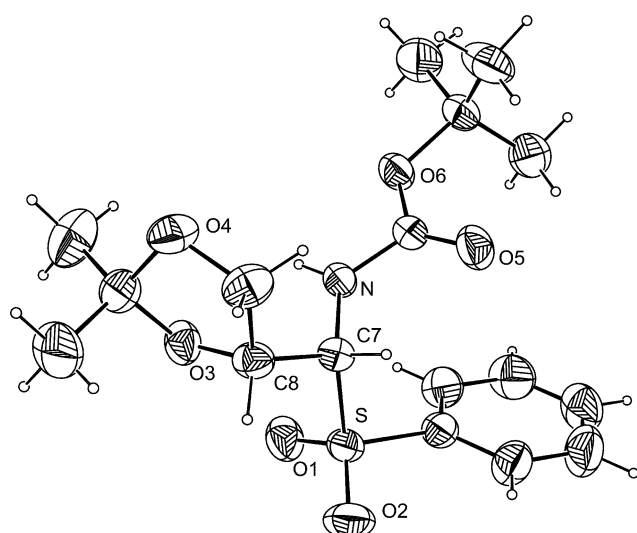
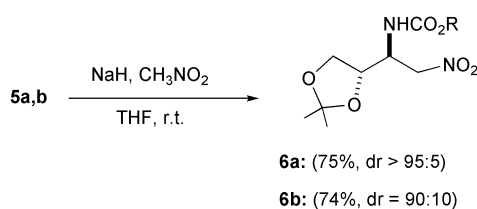


Fig. 1 X-Ray crystal structure of **5a**.



Scheme 3

The nature of the carbamoyl group affects the diastereoselectivity of the process since sulfone **5a**, which features the *N*-Boc group, is practically converted into a single *anti*-diastereomer **6a** while sulfone **5b** also produces a small amount of the *syn* diastereomer. A comparison between the stereochemical attributes of sulfone **5a** and nitro compound **6a** immediately reveals that they present an opposite stereochemistry at the newly formed stereocenter. This result is probably due to the different nature of the reactive intermediate involved in the formation of these amido derivatives. Sulfone **5a** is prepared in acidic conditions so that an *N*-acyliminium ion **7** is a likely intermediate for this process. However, nitro compound **6a** is formed in basic conditions in which the effective reactive species is an *N*-acylimine **8** (Fig. 2). Therefore, it is evident that protonation of the nitrogen atom, as occurs in *N*-acyliminium ion, would bring about a change in the conformation of the reactive intermediate thus varying the diastereofacial preference for the nucleophilic attack. PM3

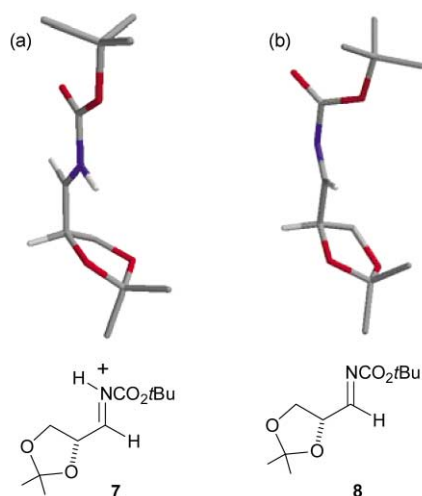


Fig. 2 PM3 lowest energy conformations for (a) *N*-acyliminium ion **7** and (b) *N*-acylimine **8**.

semiempirical calculations¹⁶ have allowed the preferred conformation of reactive intermediates *N*-acyliminium ion **7** and *N*-acylimine **8** to be established. From the structures reported in Fig. 2 it is possible to observe that the plane of hybridisation of the iminium group in **7** is rotated about 180° with respect to the same plane of the acylimine **8**. The conformation of the iminium derivative **7** is stabilized by intramolecular electrostatic interactions between the proton on nitrogen and the oxygen atoms. These interactions are also apparent in the X-ray structure of sulfone **5a** (Fig. 1).

The analysis of some transition state models for the reaction of benzenesulfonate anion with *N*-acyliminium ion intermediate **7** reveals that attack from the *Si* face requires more energy (2.90 kcal mol⁻¹) than the same approach from the *Re* side thus favoring the formation of (*R,R*)-**5a** (Fig. 3).

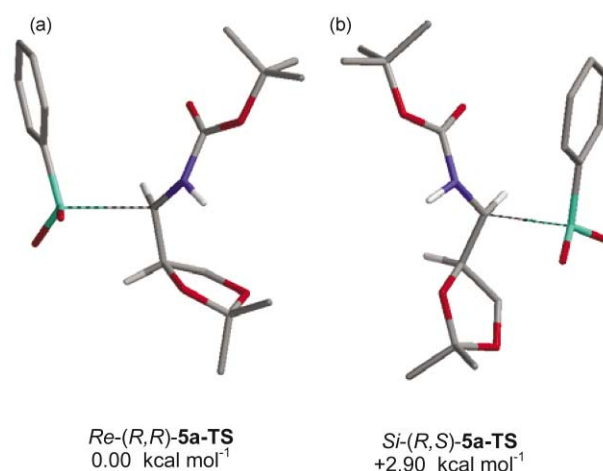


Fig. 3 PM3 minimized structures of the transition states leading to sulfones **5**. (a) (*R,R*)-**5a** and (b) (*R,S*)-**5a**.

The minimum energy conformation for the *N*-acylimine intermediate **8** shows a different arrangement of the nitrogen atom with respect to the corresponding iminium ion **7**. This conformation closely resembles that established by the Cornforth model based on dipole minimization between the ketal group C–O bond and the imino group.¹⁷ Attack of sodium methanenitronate from the *Si* face is favored by 3.92 kcal mol⁻¹ over the addition on the *Re* face and leads to the formation of (*S,S*)-**6a** (Fig. 4)

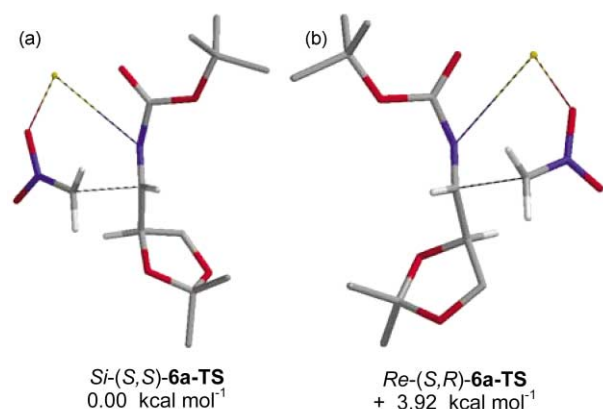
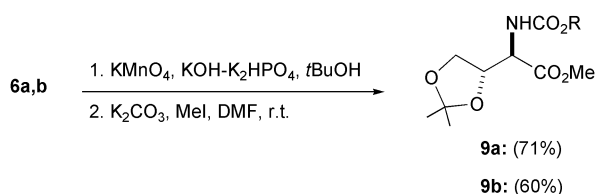


Fig. 4 PM3 minimized structures of the transition states leading to nitro derivatives **6**. (a) (*S,S*)-**6a** and (b) (*S,R*)-**6a**.

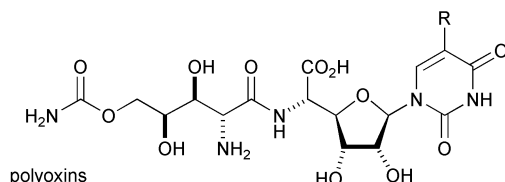
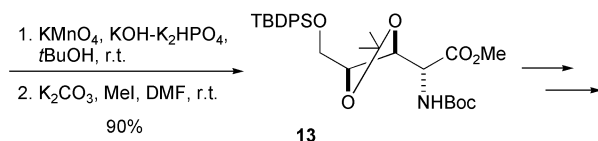
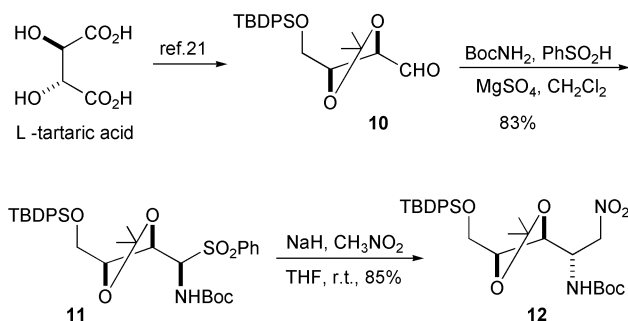
The nitro group of compound **6a** can be readily converted into a carboxylic acid by a Nef reaction using alkaline KMnO₄ solutions¹⁸ giving, after a methylation, β-hydroxy-α-amino acid esters **9** (Scheme 4).

A comparison between the literature data available for compound **9a** allowed us to establish the absolute configuration of



Scheme 4

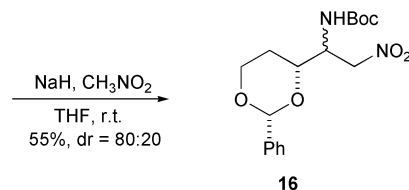
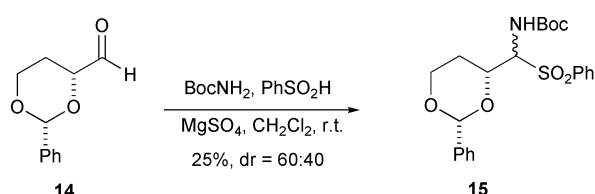
the α -amino stereocenter for esters **9**.¹⁹ It was conceivable that other chiral aldehydes structurally related to **3** could be easily converted into the corresponding sulfones. Aldehyde **10** obtained in a few steps from L-tartaric acid²⁰ gave sulfone **11** in 83% as single diastereomer (Scheme 5).



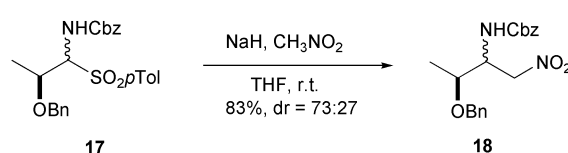
Scheme 5

The stereochemistry of the additional stereocenter in compound **11** has been inferred assuming that aldehyde **10** has a close similarity with glyceraldehyde **3**. Reaction of sulfone **11** with sodium methanenitronate gives in high yield (85%) and diastereoselectivity (>95 : 5) nitro compound **12**, which is converted into ester **13** by a Nef reaction. Polyoxamic acid ester **13** is a known intermediate in the synthesis of polyoxins, a family of antibiotics that present a specific activity against human fungal pathogens.^{20,21} The anhydrous acidic media in which the preparation of sulfones **5**, **11** takes place is unable to produce an extensive decomposition of the dioxolanyl group at least in the reduced time required for the sulfone formation. However, less stable 2-phenyl-1,3-dioxane-4-carbaldehyde **14** obtained from L-malic acid²² can be converted into the corresponding sulfone **15** only in very low yield and diastereoselectivity (25%, dr = 60 : 40) since the dioxane ring is largely cleaved giving benzaldehyde as expected by-product (Scheme 6).

The subsequent reaction with sodium methanenitronate occurs with modest yield (55%) but with a better diastereoselectivity (dr = 80 : 20) giving nitro derivative **16**. The need for a sterically demanding cyclic structure in close proximity to the reaction center is witnessed by the results obtained using sulfone **17** derived from L-O-benzylacetaldehyde that has been recently prepared by Palomo *et al.* as a mixture of diastereomers (dr = 65 : 35).²³ Reaction of sulfone **17** with the anion of nitromethane under the usual conditions only showed a modest diastereofacial selectivity affording the corresponding nitro



Scheme 6

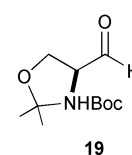


Scheme 7

derivative **18** in 83% yield as 73 : 27 mixture of inseparable diastereomers (Scheme 7).

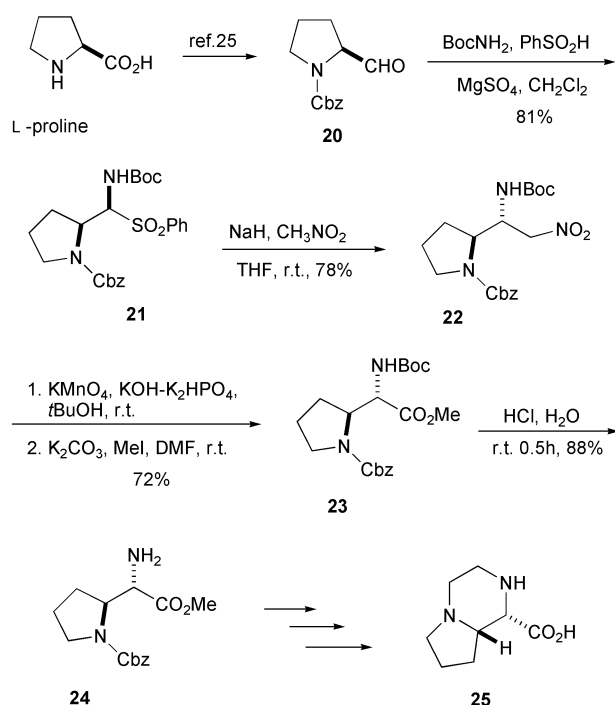
Optically active sulfones from α -amino aldehydes

Stable α -amino aldehydes²⁴ can be prepared from the corresponding α -amino acids and may represent useful substrates for the formation of α -amidoalkylphenyl sulfones. Following the interesting results obtained with chiral aldehyde **3**, we decided to use for preliminary experiments some structurally related α -amino aldehydes. However, every attempt to convert Garner's aldehyde²⁵ **19** into the corresponding sulfones using different carbamates and reaction conditions gave only disappointing results. Conversely, aldehyde **20** which is readily prepared from L-proline in a few steps²⁶ reacts under the usual conditions giving sulfone **21** in 81% yield as a sole diastereomer (Scheme 8). PM3 semiempirical calculations on intermediates **26**, **27** show a minimum energy conformation for the *N*-acyliminium ion **26** featured by hydrogen bonding between NH and carbonyl group of benzyl carbamate (Fig. 5).



A consistent rotation of the imino group is observed for *N*-acylimine **27** thus accounting for the different diastereofacial preference in the reaction with benzenesulfinate and nitromethane anions respectively.²⁷

Reaction of **21** with sodium methanenitronate gave the corresponding nitro derivative **22** as a separable mixture of diastereomers (9 : 1) with a marked preference for *anti*-**22**. Following the usual Nef reaction, nitro compound **22** has been converted into α -amino acid ester **23** in 72% yield. This derivative is a key intermediate for the preparation of piperazine-2-carboxylic acids that are useful catalysts in asymmetric reactions and are also used as chiral building blocks in the synthesis of HIV protease inhibitors. Removal of the *N*-Boc protecting group from **23** affords diamino acid ester **24** that can be transformed into piperazine **25** by a known procedure.²⁸ Sulfones obtained from linear α -amino aldehydes show a trend comparable to what is observed for compound **17** in the reaction with nitromethane anion, since they afford the corresponding nitro derivative with low diastereoselection.²⁹



Scheme 8

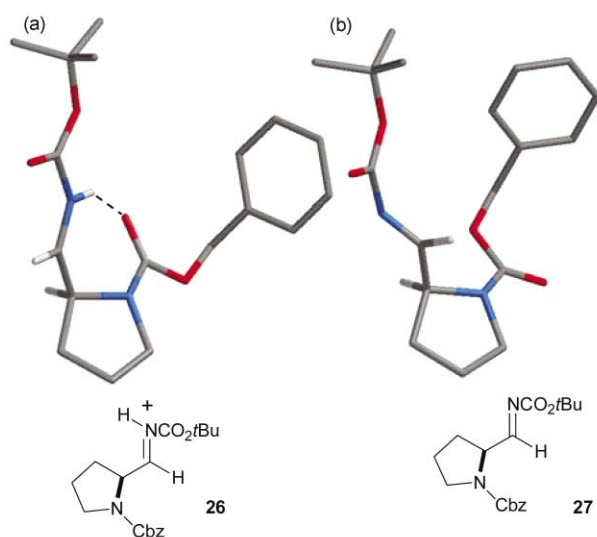


Fig. 5 PM3 lowest energy conformations for (a) *N*-acyliminium ion 26 and (b) *N*-acylimine 27.

Conclusion

In conclusion, chiral cyclic carbaldehydes can be converted into optically active α -amidoalkylphenyl sulfones generally with enhanced *syn* diastereoselectivity. These sulfones react with sodium methanidenitronate giving the corresponding *anti* nitro derivatives with high diastereoselectivity. This opposite stereoselectivity can be explained accounting for an intermediate *N*-acyliminium ion for the formation of α -amidoalkylphenyl sulfones, and a *N*-acylimine for the nitro derivative. The obtained nitro compounds can be transformed into *N*-carbamoyl- α -amino acid esters by an oxidative Nef reaction using KMnO_4 followed by a methylation. By this procedure some useful intermediates for the synthesis of biologically active compounds can be prepared. The same synthetic strategy works less efficiently when sulfones obtained from linear aldehydes are used in the reaction with nitromethane anion. Preliminary experiments with other nitro compounds reveal that they react sluggishly with α -amidoalkylphenyl sulfones giving modest results in terms of yield and diastereoselectivity. However it is

conceivable that a range of different nucleophilic reagents can be profitably added to these chiral sulfones with good diastereoselectivity thus expanding the significance of the present procedure to the preparation of other useful synthetic intermediates.

Experimental

^1H NMR were recorded at 300 MHz on a Varian VXR300 in CDCl_3 as solvent. ^{13}C NMR were recorded at 75 MHz in CDCl_3 as solvent. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Microanalyses were performed with a CHNS-O analyzer Model EA 1108 from Fisons Instruments. IR spectra were recorded with a Perkin-Elmer Paragon 500 FT-IR. GLC analyses were performed on a Hewlett-Packard 5890 equipped with a capillary column of fused silica (0.32 mm \times 25 m), stationary phase SE54. Mass spectra were performed on a Hewlett-Packard GC/MS 5970 by means of the EI technique (70 eV). Crystals suitable for X-ray structure determination were mounted on a Bruker AXS SMART 2000 CCD diffractometer and irradiated with graphite monochromated Mo-K α radiation. Tetrahydrofuran was dried by refluxing it over sodium wire and then distilled. Dichloromethane was dried by refluxing it over calcium hydride and then distilled. All chemicals used are commercial.

Crystal structure determination of compound 5a

Crystal data. $\text{C}_{17}\text{H}_{25}\text{NO}_6\text{S}$, $M = 371.45$, orthorhombic system, space group $P2_12_12_1$, $a = 9.9643(4)$ Å, $b = 11.1330(4)$ Å, $c = 17.3159(7)$ Å, $V = 1920.9(1)$ Å 3 , $Z = 4$, $\rho_{\text{calc}} = 1.284$ Mg m $^{-3}$, $R = 0.0358$ ($R^2_w = 0.0931$) for 5339 observed reflections (214 parameters) with $I > 2\sigma I$. Goodness of fit = 1.086. Flack 0.00(0.04). ‡

General procedure for the preparation of phenylsulfonyl derivatives

Carbamate **4** (6 mmol) was dissolved in dichloromethane (30 cm 3) and then benzenesulfinic acid (7.5 mmol), the appropriate aldehyde (5 mmol) and anhydrous MgSO_4 (0.5 g) were sequentially added at room temperature. The mixture was stirred for 2 h (16 h for compound **21**) at room temperature and then filtered over a short pad of Florisil. Removal of the solvent afforded the crude sulfone which was purified by column chromatography (7 : 3 hexanes–ethyl acetate).

***tert*-Butyl *N*-[(*R*)-1-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-(phenylsulfonyl)methyl]carbamate 5a.** Yield 75%. Mp: 135 °C. $[\alpha]_D^{20} = -6.3$ (c 0.85, CHCl_3). Found C, 55.05; H, 6.74; N, 3.81. Calc. for $\text{C}_{17}\text{H}_{25}\text{NO}_6\text{S}$ C, 54.97; H, 6.78; N, 3.77%. ν_{max} (KBr)/cm $^{-1}$ 3450, 1695, 1375, 1145. δ_{H} (300 MHz; CDCl_3) 1.24 (s, 3H, rotamer A), 1.26 (s, 3H, rotamer B), 1.32 (s, 3H, rotamer A), 1.40 (s, 9H, rotamer B), 1.44 (s, 9H, rotamer A), 3.74 (dd, 1H, $J = 6.6, 8.4$ Hz), 5.05–4.23 (m, 2H), 4.76–5.10 (m, 1H), 5.43 (d, 1H, $J = 10.3$ Hz, rotamer B), 5.50 (d, 1H, $J = 10.3$ Hz, rotamer A), 7.50–7.68 (m, 3H), 7.88–7.93 (m, 2H). δ_{C} (75 MHz; CDCl_3) 25.1, 25.3, 26.3, 26.6 (CH_3 acetal), 27.9, 28.2, 28.5, 29.5 (CH_3 *t*-Bu), 65.7, 67.2 (CH_2O), 70.7, 70.9 (CHO), 72.0, 72.1 (CHN), 81.3, 81.4 (*C t*-Bu), 110.3, 111.1 (OCO), 129.2, 129.3, 129.4, 129.5, 134.2, 134.3, 137.3, 137.8 (*C* arom.), 154.2, 154.3 (*C=O*).

Benzyl *N*-[(*R*)-1-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-(phenylsulfonyl)methyl]carbamate 5b. Yield 70%. Mp: 90 °C. $[\alpha]_D^{20} = +0.6$ (c 0.5, CHCl_3). Found C, 59.19; H, 5.77; N, 3.41. Calc. for $\text{C}_{20}\text{H}_{23}\text{NO}_6\text{S}$ C, 59.24; H, 5.72; N, 3.45%. ν_{max} (KBr)/cm $^{-1}$ 3380, 1695, 1375, 1145. δ_{H} (300 MHz; CDCl_3) 1.40 (s, 3H),

‡ CCDC reference number 216822. See <http://www.rsc.org/suppdata/ob/b3/b309211a/> for crystallographic data in .cif or other electronic format.

1.42 (s, 3H), 3.75 (dd, 1H, $J = 6.3, 8.7$ Hz), 4.17–4.26 (m, 2H), 4.83–5.02 (m, 3H), 5.68 (d, 1H, $J = 10.3$ Hz), 7.18–7.70 (m, 8H), 7.85–7.96 (m, 2H). δ_{C} (75 MHz; CDCl_3) 25.2, 26.3 (CH_3 acetal), 67.2 (PhCH_2), 67.8 (CH_2O), 70.7, 71.4 (CHO), 72.0, 72.4 (CHN), 110.3 (OCO), 128.3, 128.6, 128.8, 129.3, 129.4, 129.5, 134.5, 134.7, 136.9 (C arom.), 154.3 (C=O).

tert-Butyl *N*-[(*R*)-1-[(4*R*,5*R*)-5-[(1-*tert*-butyl)-1,1-diphenylsilyl]oxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-(phenylsulfonyl)methyl]carbamate 11. Yield 83%. Waxy solid. $[\alpha]_{\text{D}}^{20} = -20.8$ (c 1.3, CHCl_3). Found C, 63.90; H, 7.04; N, 2.22. Calc. for $\text{C}_{34}\text{H}_{45}\text{NO}_7\text{SSi}$ C, 63.82; H, 7.09; N, 2.19%. ν_{max} (film)/ cm^{-1} 3400, 1695, 1375, 1145. δ_{H} (300 MHz; CDCl_3) 1.06 (s, 9H, rotamer A), 1.08 (s, 9H, rotamer B), 1.23 (s, 6H, rotamer A), 1.25 (s, 6H, rotamer B), 1.44 (s, 9H), 3.71–3.90 (m, 3H), 5.01–5.15 (m, 2H), 5.65 (d, 1H, $J = 10.3$), 7.38–7.56 (m, 7H), 7.60–7.76 (m, 6H), 7.86–7.95 (m, 2H). δ_{C} (75 MHz; CDCl_3) 19.4 (SiCMe_3), 26.9, 27.1 (CH_3 acetal), 27.2 (CH_3 *t*-BuSi), 28.2 (CH_3 *t*-BuO), 64.0 (CH_2OSi), 70.4 (CHN), 74.2 (OCHCH_2), 77.7 (OCHCH), 81.1 (OCMe_3), 111.3 (OCO), 128.0, 128.1, 129.0, 129.2, 129.5, 130.1, 134.2, 135.9 (C arom.), 154.2 (C=O).

tert-Butyl *N*-[(2-phenyl-1,3-dioxan-4-yl)(phenylsulfonyl)methyl]carbamate 15. Yield 25%. Mp: 76 °C. Found C, 60.91; H, 6.31; N, 3.20. Calc. for $\text{C}_{22}\text{H}_{27}\text{NO}_6\text{S}$ C, 60.95; H, 6.28; N, 3.23%. ν_{max} (KBr)/ cm^{-1} 3450, 1695, 1375, 1145. δ_{H} (300 MHz; CDCl_3) (diastereomer A) 1.44 (s, 9H), 1.90–2.21 (m, 2H), 3.95–4.15 (m, 2H), 4.98–5.10 (m, 1H), 5.50–5.58 (m, 1H), 5.74–5.83 (m, 1H), 6.08–6.17 (m, 1H), 7.30–7.70 (m, 8H), 7.86–7.95 (m, 2H). (diastereomer B) 1.46 (s, 9H), 1.90–2.21 (m, 2H), 4.25–4.40 (m, 2H), 4.75–4.88 (m, 1H), 5.61–5.70 (m, 1H), 5.85–5.99 (m, 1H), 6.08–6.17 (m, 1H), 7.30–7.70 (m, 8H), 7.86–7.95 (m, 2H).

Benzyl (2*S*)-2-[(*R*)-1-[(*tert*-butoxycarbonyl)amino]-1-(phenylsulfonyl)methyl]tetrahydro-1*H*-1-pyrrolecarboxylate 21. Yield 81%. Mp: 112 °C. $[\alpha]_{\text{D}}^{20} = -50.1$ (c 0.85, CHCl_3). Found C, 60.79; H, 6.40; N, 5.86. Calc. for $\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}_6\text{S}$ C, 60.74; H, 6.37; N, 5.90%. ν_{max} (KBr)/ cm^{-1} 3320, 1695, 1375, 1145. δ_{H} (300 MHz; CDCl_3) 1.14 (s, 9H), 1.80–2.25 (m, 2H), 2.38–2.60 (m, 1H), 3.30–3.55 (m, 2H), 4.58–4.80 (m, 2H), 5.05–5.22 (m, 3H), 6.21 (d, 1H, $J = 9.2$ Hz), 7.30–7.70 (m, 8H), 7.78–7.98 (m, 2H). δ_{C} (75 MHz; CDCl_3) 23.6 ($\text{CH}_2\text{CH}_2\text{N}$), 28.1 (CH_3 *t*-Bu), 29.9 (CH_2CHN), 46.5 (CH_2N), 55.6 (CHN), 67.5 (ArCH_2), 74.0 (CHNH), 80.5 (OCMe_3), 128.0, 128.3, 128.7, 128.9, 129.7, 134.0, 136.6, 137.5 (C arom.), 154.6 (NHC=O), 157.1 (NC=O).

General procedure for the preparation of nitro derivatives

To a stirred suspension of NaH (25 mmol) in dry THF (15 cm^3), nitromethane (25 mmol) was added dropwise at room temperature. After stirring for 30 min, the appropriate sulfone (5 mmol) dissolved in dry THF (8 cm^3) was added and the white suspension was stirred at room temperature for 30 min. The reaction was quenched by addition of satd NH_4Cl (8 cm^3), extracted with CHCl_3 (4 \times 15 cm^3) and then dried over MgSO_4 . The crude nitro derivative obtained after removal of the solvent was purified by column chromatography (7 : 3 hexanes–ethyl acetate).

tert-Butyl *N*-(1*S*)-1-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-nitroethylcarbamate 6a. Yield 75%. Oil. $[\alpha]_{\text{D}}^{20} = -13.5$ (c 1, CHCl_3). Found C, 49.59; H, 7.68; N, 9.70. Calc. for $\text{C}_{12}\text{H}_{22}\text{N}_2\text{O}_6$ C, 49.65; H, 7.64; N, 9.65%. ν_{max} (film)/ cm^{-1} 3420, 1700, 1650, 1550. δ_{H} (300 MHz; CDCl_3) 1.33 (s, 3H), 1.44 (s, 12H), 3.91 (dd, 1H, $J = 4.4, 8.8$ Hz), 4.10 (dd, 1H, $J = 6.2, 8.8$ Hz), 4.02–4.18 (m, 1H), 4.20–4.35 (m, 1H), 4.60 (dd, 1H, $J = 3.3, 13.6$ Hz), 4.74 (dd, 1H, $J = 5.5, 13.6$ Hz), 5.06 (d, 1H, $J = 9.2$ Hz). δ_{C} (75 MHz; CDCl_3) 25.3, 26.7 (CH_3 acetal), 28.4 (CH_3 *t*-Bu), 63.8

(CHNH), 66.4 (OCH), 66.7 (OCH_2), 77.9 (CH_2NO_2), 79.8 (OCMe_3), 109.9 (OCO), 155.5 (C=O).

Benzyl *N*-(1*S*)-1-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-nitroethylcarbamate 6b. Yield 74%. Mp 77 °C. $[\alpha]_{\text{D}}^{20} = +7.9$ (c 0.85, CHCl_3). Found C, 55.49; H, 6.18; N, 8.60. Calc. for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_6$ C, 55.55; H, 6.22; N, 8.64%. ν_{max} (KBr)/ cm^{-1} 3420, 1700, 1650, 1550. δ_{H} (300 MHz; CDCl_3) 1.33 (s, 3H), 1.44 (s, 3H), 3.90 (dd, 1H, $J = 4.0, 8.8$ Hz), 4.06–4.48 (m, 3H), 4.62 (dd, 1H, $J = 3.3, 13.9$ Hz), 4.76 (dd, 1H, $J = 5.9, 13.8$ Hz), 5.12 (s, 2H), 5.40 (d, 1H, $J = 10.4$ Hz), 7.31–7.43 (m, 5H). δ_{C} (75 MHz; CDCl_3) 25.0, 26.8 (CH_3 acetal), 52.6 (CHNH), 67.3 (PhCH_2), 67.7 (OCH_2CH), 74.9 (OCH), 75.3 (CH_2NO_2), 110.7, 128.4, 128.6, 128.8, 128.9 (C arom.), 154.3 (C=O).

tert-Butyl *N*-(1*S*)-1-[(4*S*,5*R*)-5-[(1-*tert*-butyl)-1,1-diphenylsilyl]oxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-nitroethylcarbamate 12. Yield 85%. Oil. $[\alpha]_{\text{D}}^{20} = -3.4$ (c 1, CHCl_3). Found C, 62.40; H, 7.55; N, 4.97. Calc. for $\text{C}_{29}\text{H}_{42}\text{N}_2\text{O}_7\text{Si}$ C, 62.34; H, 7.58; N, 5.01%. ν_{max} (film)/ cm^{-1} 3420, 1700, 1650, 1550. δ_{H} (300 MHz; CDCl_3) 1.08 (s, 9H), 1.36 (s, 3H), 1.40 (s, 3H), 1.43 (s, 9H), 3.73 (dd, 1H, $J = 3.7, 11.0$ Hz), 3.83 (dd, 1H, $J = 4.4, 11.0$ Hz), 4.11–4.30 (m, 3H), 4.65–4.69 (m, 2H), 4.90 (d, 1H, $J = 8.6$ Hz), 7.35–7.50 (m, 6H), 7.68–7.78 (m, 4H). δ_{C} (75 MHz; CDCl_3) 19.4 (SiCMe_3), 27.1, 27.4 (CH_3 acetal), 27.6 (CH_3 *t*-BuSi), 28.4 (CH_3 *t*-BuO), 52.2 (CHNH), 64.1 (CH_2OSi), 75.9 (CH_2NO_2), 76.0 (OCHCH_2), 77.7 (OCHCH), 80.3 (Me_3CO), 110.5 (OCO), 125.5, 128.0, 128.1, 129.3, 130.1, 130.2, 135.8, 135.9 (C arom.), 154.1 (C=O).

tert-Butyl *N*-[2-nitro-1-(2-phenyl-1,3-dioxan-4-yl)ethyl]carbamate 16. Yield 55%. Mp: 88 °C. $[\alpha]_{\text{D}}^{20} = -44.5$ (c 2.1, CHCl_3). Found C, 57.99; H, 6.81; N, 7.97. Calc. for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_6$ C, 57.94; H, 6.86; N, 7.95%. ν_{max} (KBr)/ cm^{-1} 3420, 1700, 1650, 1550. δ_{H} (300 MHz; CDCl_3) (major diastereomer) 1.45 (s, 9H), 1.68–2.00 (m, 2H), 3.95 (dt, 1H, $J = 3.0, 11.7$ Hz), 4.01–4.17 (m, 1H), 4.21–4.40 (m, 2H), 4.63 (dd, 1H, $J = 3.7, 13.5$ Hz), 4.84 (dd, 1H, $J = 6.6, 13.5$ Hz), 5.22 (d, 1H, $J = 10.4$ Hz), 5.47 (s, 1H), 7.35–7.48 (m, 5H). δ_{C} (75 MHz; CDCl_3) (major diastereomer) 28.4 (CH_3 *t*-Bu), 39.6 ($\text{CH}_2\text{CH}_2\text{CH}$), 52.9 (CHNH), 66.9 (OCH_2), 74.9 (CH_2NO_2), 76.4 ($\text{CH}_2\text{CH}_2\text{CH}$), 80.8 (Me_3CO), 101.5 (OCHO), 126.2, 128.5, 129.3, 138.0 (C arom.), 155.3 (C=O).

Benzyl *N*-[2-(benzyloxy)-1-(nitromethyl)propyl]carbamate 18. Yield 83%. Oil. Found C, 63.55; H, 6.48; N, 7.76. Calc. for $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}_5$ C, 63.50; H, 6.45; N, 7.79%. ν_{max} (film)/ cm^{-1} 3420, 1700, 1652, 1553. δ_{H} (300 MHz; CDCl_3) 1.26 (d, 3H, $J = 6.2$ Hz, minor diast.), 1.29 (d, 3H, $J = 6.2$ Hz, major diast.), 3.70–3.80 (m, 1H), 4.22–4.40 (m, 2H), 4.56–4.74 (m, 3H), 5.04–5.16 (m, 2H), 5.38 (d, 1H, $J = 9.5$ Hz, minor diast.), 5.57 (d, 1H, $J = 9.4$ Hz, major diast.), 7.28–7.40 (m, 10H). δ_{C} (75 MHz; CDCl_3) (major diastereomer) 16.6 (CH_3), 54.5 (CHNH), 67.4 ($\text{CH}_2\text{OC=O}$), 71.3 (CH_3CH), 74.8 (CH_2OCH), 75.2 (CH_2NO_2), 128.1, 128.2, 128.3, 128.5, 128.8, 136.4, 137.8 (C arom.), 156.0 (C=O).

Benzyl (2*S*)-2-[(1*R*)-1-[(*tert*-butoxycarbonyl)amino]-2-nitroethyl]tetrahydro-1*H*-1-pyrrolecarboxylate 22. Yield 78%. Oil. $[\alpha]_{\text{D}}^{20} = -30.1$ (c 0.45, CHCl_3). Found C, 58.06; H, 6.88; N, 6.96. Calc. for $\text{C}_{19}\text{H}_{27}\text{N}_3\text{O}_6$ C, 58.00; H, 6.92; N, 7.00%. ν_{max} (film)/ cm^{-1} 3420, 1700, 1650, 1550. δ_{H} (300 MHz; CDCl_3) 1.43 (s, 9H, rotamer A), 1.45 (s, 9H, rotamer B), 1.80–2.22 (m, 4H), 3.31–3.63 (m, 2H), 4.01–4.17 (m, 1H), 4.21–4.40 (m, 1H), 4.42–4.70 (m, 2H), 5.14 (s, 2H), 5.35–5.50 (m, 1H, rotamer A), 5.60–5.75 (m, 1H, rotamer B), 7.30–7.45 (m, 5H). δ_{C} (75 MHz; CDCl_3) 27.1 ($\text{CH}_2\text{CH}_2\text{N}$), 28.4 (CH_3 *t*-Bu), 47.5 (CH_2N), 54.3 (CHNH), 58.7 (PhCH_2O), 67.7 (CHN), 79.7 (CH_2NO_2), 81.8 (Me_3C), 128.1, 128.4, 128.8, 136.5 (C arom.), 155.4 (NHC=O), 156.3 (NC=O).

General procedure for the preparation of amino acid esters

Nitro derivative (1 mmol) dissolved in *t*BuOH (8 cm³) was treated with aqueous buffered KOH (0.5 M in KOH and 1.25 M in K₂HPO₄, 6 cm³) at room temperature. The mixture was stirred for 5 min and then aqueous KMnO₄ (0.5 M, 2 cm³, 4 mmol) was added dropwise maintaining the temperature below 25 °C by occasional cooling. After stirring at room temperature for 1 h the mixture was cooled by ice bath and then satd Na₂SO₃ (10 cm³) was added. The mixture was then acidified with 2 M HCl until pH ~ 5 and then extracted with ethyl acetate (4 × 15 mL). The organic solution was dried over MgSO₄ and after evaporation of the solvent the crude acid was obtained. The acid was dissolved in dry DMF (5 cm³) and K₂CO₃ (3 mmol) and MeI (2 mmol) were sequentially added. The mixture was stirred for 30 min and then was poured into cold water (20 cm³). The solution was extracted with CHCl₃ (4 × 15 cm³) and the organic phase was dried over MgSO₄. Evaporation of the solvent gave crude amino acid ester, which was purified by column chromatography (6 : 4 hexanes–ethyl acetate).

Methyl (2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]ethanoate 9a. Yield 71%. Oil. [α]_D²⁰ = –37.3 (*c* 2, CHCl₃) [lit.¹⁹ [α]_D²⁰ = –33.5 (*c* 1.6, CHCl₃)]. Spectroscopic data are in agreement with those reported in literature.

Methyl (2*R*)-2-[(benzyloxy)carbonyl]amino-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]ethanoate 9b. Yield 60%. Oil. [α]_D²⁰ = –25.3 (*c* 1.2, CHCl₃). Found C, 59.50; H, 6.61; N, 4.28. Calc. for C₁₆H₂₁NO₆ C, 59.43; H, 6.55; N, 4.33%. ν_{\max} (film)/cm^{–1} 3420, 1735. δ_{H} (300 MHz; CDCl₃) 1.32 (s, 3H), 1.38 (s, 3H), 3.77 (s, 3H), 4.03–4.16 (m, 2H), 4.37 (q, 1H, *J* = 4.4 Hz), 4.48 (dd, 1H, *J* = 4.4, 8.4 Hz), 5.12 (s, 2H), 5.58 (d, 1H, *J* = 8.4 Hz), 7.30–7.38 (m, 5H). δ_{C} (75 MHz; CDCl₃) 24.9, 26.4 (CH₃ acetal), 52.7 (CH₃O), 56.4 (CHNH), 65.9 (PhCH₂), 67.4 (CH₂OC), 76.4 (CHOC), 110.4 (OCO), 128.3, 128.4, 128.7, 136.2 (*C* arom.), 156.0 (NHC=O), 170.3 (CO₂Me).

Methyl (2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-[(4*S*,5*R*)-5-[(1-(*tert*-butyl)-1,1-diphenylsilyl]oxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]ethanoate 13. Yield 90%. Mp 87 °C. [α]_D²⁰ = –25.2 (*c* 3, CHCl₃). [lit.²⁰: oil, [α]_D²⁷ = –26.2 (*c* 1.02, CHCl₃)]. Found C, 64.68; H, 7.82; N, 2.48. Calc. for C₃₀H₄₇NO₇Si C, 64.60; H, 7.77; N, 2.51%. ν_{\max} (KBr)/cm^{–1} 3420, 1735. δ_{H} (300 MHz; CDCl₃) 1.06 (s, 9H), 1.36 (s, 3H), 1.38 (s, 3H), 1.42 (s, 9H), 3.73 (s, 3H), 3.67–3.82 (m, 2H), 4.20–4.30 (m, 2H), 4.45–4.50 (m, 1H), 5.27 (d, 1H, *J* = 10.4 Hz), 7.35–7.44 (m, 6H), 7.64–7.77 (m, 4H). δ_{C} (75 MHz; CDCl₃) 19.4 (Me₃CSi), 27.0 (CH₃ *t*-BuSi), 27.3, 27.5 (CH₃ acetal), 28.5 (CH₃ *t*-BuO), 52.6 (CH₃O), 55.7 (CHNH), 63.8 (CH₂O), 78.5 (OCHCH), 78.6 (OCHCH₂), 80.4 (Me₃CO), 110.2 (OCO), 128.0, 129.9, 133.2, 135.1, 135.9 (*C* arom.), 155.3 (NHC=O), 170.7 (CO₂Me).

Benzyl (2*S*)-2-[(1*R*)-1-[(*tert*-butoxycarbonyl)amino]-2-methoxy-2-oxoethyl]tetrahydro-1*H*-1-pyrrolicarboxylate 23. Yield 72%. Oil. [α]_D²⁰ = –34.8 (*c* 2.5, CHCl₃). Found C, 61.15; H, 7.14; N, 7.09. Calc. for C₂₀H₂₈N₂O₆ C, 61.21; H, 7.19; N, 7.14%. ν_{\max} (film)/cm^{–1} 3420, 1735. δ_{H} (300 MHz; CDCl₃) 1.43 (s, 9H), 1.80–2.05 (m, 4H), 3.30–3.68 (m, 2H), 3.76 (s, 3H), 4.25–4.37 (m, 2H), 5.13 (s, 2H), 5.65–5.75 (m, 1H), 7.30–7.43 (m, 5H). δ_{C} (75 MHz; CDCl₃) 23.9 (CH₂CH₂N), 28.5 (CH₃ *t*-Bu), 29.2 (CH₂CHN), 47.4 (CH₃O), 52.6 (CH₂N), 57.7 (CHNH), 59.2 (PhCH₂), 67.4 (CHN), 80.1 (Me₃C), 128.1, 128.3, 128.7, 136.9 (*C* arom.), 165.2, 166.8 (C=O carb.), 171.9 (CO₂Me).

Benzyl (2*S*)-2-[(1*R*)-1-amino-2-methoxy-2-oxoethyl]tetrahydro-1*H*-1-pyrrolicarboxylate 24. *N*-Boc amino ester 23

(0.31 g, 0.8 mmol) was dissolved in THF (8 cm³) and 37% HCl (4 cm³) was then added at room temperature. The mixture was stirred for 30 min at room temperature, cooled by ice bath and made alkaline by addition of NaOH pellets. The solution was then extracted with ethyl acetate (4 × 10 cm³) and dried over Na₂SO₄. After evaporation of the solvent at reduced pressure the crude product was purified by column chromatography (98 : 2 ethyl acetate–methanol) giving 0.2 g (88%) of pure amino ester 24 as a clear oil. [α]_D²⁰ = –20.7 (*c* 6, EtOH) [lit.²⁸ [α]_D²⁰ = –19.6 (*c* 1.03, CHCl₃)]. Spectroscopic data are in agreement with those reported in literature.

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