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The first synthesis of N,O-protected $\beta^{2,2,3,3}$-isoserines bearing two adjacent quaternary stereogenic centers and their corresponding β-lactams

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Abstract—The reaction of chiral (2*S*)-enolates of dioxolan-4-ones, derived from lactic and mandelic acids, with (S_R)-*tert*-butyl sulfinyl ketimines, derived from butan-2-one, pentan-2-one, and decan-2-one, afforded conformationally restrained $\beta^{2,2,3,3}$-isoserines bearing two adjacent quaternary stereogenic centers in the form of *N*-sulfinyl protected 1′-amino-dioxolan-4-ones. The selective acid-induced removal of the sulfinyl protecting group provided the corresponding 1′-aminodioxolanones, whose base-induced cyclization afforded the corresponding chiral tetra-substituted 3-hydroxy-β-lactams. The synthesis of a dipeptide by reaction coupling between the 1′-aminodioxolanone (2*S*,5*R*,1′*R*)-**19** and *N*,*N*-dimethylglycine was successfully achieved.

1. Introduction

β-Amino acids are important constituents of biologically active natural products and pharmaceutical agents,[1] as well as valuable precursors to these structures, such as β-lactams. In addition, oligomers of β-amino acids, for example, β-peptides,[2] have attracted attention as useful peptidomimetics because of their proteolytic stability relative to natural α-peptides and their propensity to adopt stable secondary structures. Particular attention has been lately devoted to the asymmetric synthesis of β-amino acids containing quaternary $\beta^{2,2}$ or $\beta^{3,3}$ stereogenic centers,[3,4] due to their resistance to proteolytic degradation, which render them excellent building blocks for bioactive molecules synthesis.[3] However, structural studies on their peptidomimetics are lacking, due to the limited availability of these molecules in stereoisomerically pure form. Even more difficult is the preparation of tetra-substituted enantiopure $\beta^{2,2,3,3}$-amino acids, since the control of stereoselectivity in reactions generating two adjacent quaternary stereogenic centers still represents a synthetic challenge. To date, the only known methodology for the synthesis of $\beta^{2,2,3,3}$-amino acids is the addition of titanium enolates to *N*-sulfinyl ketimines reported by Elmann's group,[4c] although this strategy only provides one stereogenic center at the $\beta^{3,3}$ position. In this Letter, we describe the first synthesis of enantiopure β-amino acids, bearing two adjacent quaternary stereogenic centers in their backbone ($\beta^{2,2,3,3}$-isoserines). The isoserine pattern is found in a variety of natural products and pharmaceutical agents like taxoids,[5] GABOB,[6] and aminopeptidase inhibitors (bestatin,[7] probestatin,[7] phebestatin,[7] the bestatin-type MetAP2 inhibitor A-357300,[8] and amastatin[9]). Furthermore, they can be employed as building blocks for oligopeptides synthesis[10] and constrained analogues of biologically active compounds.[11] It is worth noting that chiral $\beta^{2,2,3,3}$-isoserines bear several structural features, which reveal to be very useful in terms of folding patterns of the corresponding peptides, such as the presence of the polar H-bonding donor/acceptor β^2-hydroxy substituent, the presence of dissimilar hydrophobic groups at the two quaternary stereogenic centres, as well as the possibility to obtain *syn*/*anti* β^2,β^3-configurational stereoisomers.

A fine tuned combination of these parameters can provide significant structural diverse β-amino acids, which will influence the characteristics of their derivatives, β-peptides. For instance, modifications have been

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observed in some hexapeptide structures when assembled with $\beta^{2,3,3}$-isoserine frames,[12,13] namely, conformational analyses of a very soluble (2*R*,3*S*)-norstatine based hexapeptide established that its structure was a right-handed helix,[14] while the replacement of the hydroxyl group with a methyl led to an insoluble analogue with a pleated-sheet conformation.[3b]

The following study will present an investigation on the synthesis of tetra-substituted enantiopure *syn*/*anti* $\beta^{2,2,3,3}$-isoserines, by using a protocol already experimented for tri-substituted analogues.[15] For this purpose, the (2*S*)-enolate of 1,3-dioxolan-4-ones were reacted with *N*-sulfinyl ketimines to afford N,O-orthogonally protected 1′-sulfinylamino-dioxolanones. Besides, their conversion into the corresponding C3,C4-tetra-substituted β-lactams will be reported. In fact, it has been demonstrated that lipophilic monobactams show cytotoxic[16] or inhibitory cholesterol absorption activity.[17] Finally, this preliminary study paves the way for further investigations on the efficiency of coupling reactions toward the synthesis of $\beta^{2,2,3,3}$-isoserine-based peptides.

2. Synthesis of (S_S)- and (S_R)-1′-sulfinylamino-dioxolan-ones

Based on their different steric demand, dioxolanones (2*S*,5*S*)-**1**[18] and (2*S*,5*S*)-**2**[19] were selected for this study. Treatment of the dioxolanones with lithiated bases afforded the corresponding (2*S*)-chiral enolates **1a** and **2a**, respectively. (S_R)-*N*-*tert*-butyl sulfinyl ketimines **3**–**5** (Fig. 1)[20] were selected as the enolates reaction partners, since preliminary investigations employing (S_S)-*N*-*tert*-butyl sulfinyl ketimines **3** and **4** only provided poor results in terms of either chemical yields (20–30%) or selectivities. In fact only a complex mixture of three diastereoisomers, derived from transition states TS I-TS III, was obtained.[21]

Ketimines **3**–**5** were prepared by condensation of (*R*)-*tert*-butyl sulfinyl amide with the unbranched aliphatic ketones: butan-2-one, pentan-2-one, and decan-2-one.[22,23] The use of the sulfinyl protecting group provides stable electrophilic ketimines, avoiding their well known rapid isomerization to non-reactive enamines under basic conditions.

^{1}H NMR spectroscopy data showed that (*R*)-**3** was obtained as a 9:1 (*E*/*Z*) mixture, while (*R*)-**4** and (*R*)-**5** were obtained as a 5:1 (*E*/*Z*) mixture. From a stereochemical point of view, the addition of (S_R)-sulfinyl ketimines to

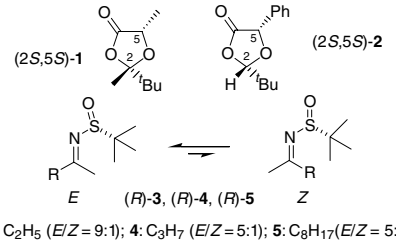
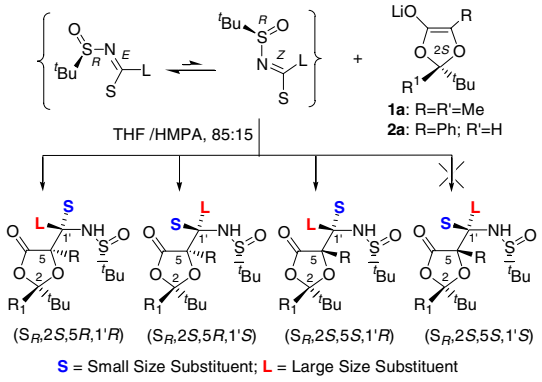


Figure 1. Dioxolanones **1** and **2** and *E*/*Z* -(*R*)-ketimines **3**–**5**.



Scheme 1.

(2*S*)-enolates can provide four diastereoisomers, whose relative distribution depends on two different factors: face selectivity, which controls the stereogenic center at the 5-position, while *exo*/*endo* simple selectivity rules the newly formed C1′-carbon stereocenter (Scheme 1).

As reported in Table 1 (entries 1–3), enolate (2*S*)-**1a** approaches the ketimines from the less hindered diastereotopic face, thus only the diastereoisomers derived from TS I (S_R,2*S*,5*R*,1′*R*-configuration, major) and TS II (S_R,2*S*,5*R*,1′*S*-configuration, minor) were formed.

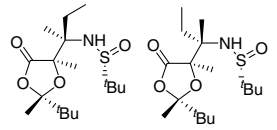
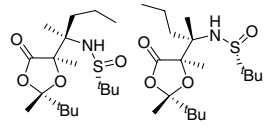
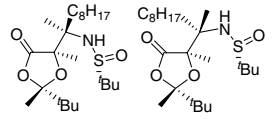
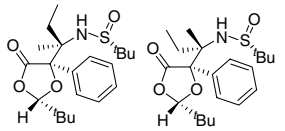
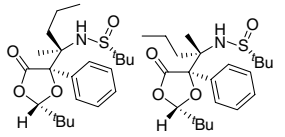
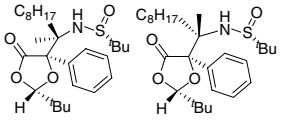
The stereochemistry at the 1′ position strongly depends on reagents steric requirements. When enolate (2*S*)-**1a** was used as a reaction partner, the selectivity was directed by the small methyl substituent at the C-5 carbon atom of the enolate, favoring an *exo* approach of the imine to the dioxolanone ring with the formation of the S_R,2*S*,5*R*,1′*R*-isomers **6**, **8**, and **10** as major products (Table 1). On the other hand, when enolate (2*S*)-**2a**, which bears the more steric demanding phenyl group at C5 and the smaller hydrogen atom at C2 positions, was employed the diastereofacial selectivity was reversed. Thus, (S_S,2*S*,5*R*,1′*S*)-isomers **12**, **14**, and **16** were obtained with very high de. Separation of the isomeric pairs (**10**/**11**), (**12**/**13**), (**14**/**15**), and (**16**/**17**) was performed by silica gel column chromatography (cyclohexane/acetone, 9:1), while any attempts to separate **6**/**7** and **8**/**9** pairs failed. Structural characterization of all compounds was carried out by ^{1}H and ^{13}C NMR spectroscopy. In particular, ^{1}H NMR-NOE experiments allowed the assignment of their (5*R*)-stereochemistry.

3. Chemistry of the 1′-sulfinylamino-dioxolanones

In the second part of the present work, we focused our attention on the selective nitrogen deprotection of derivatives **6**–**17**, and the following transformation of the free amines **18**–**25** into the corresponding tetrasubstituted lypophilic β-lactams **26**–**31** (Table 2).

Sulfinyl protecting group removal for pure compounds **10**, **11**, **13**, **15**, **17** and **6**/**7** and **8**/**9** mixtures was carried out with 2 N HCl in 1:1 MeOH/Et_2O mixed solvent, affording the corresponding N-unprotected 1′-amino-

Table 1. Products distribution for the reaction of (2S)-enolates **1a** and **2a** with (*R*)-configured ketimines **3**–**5**

Entry	(2*S*)-Enolate	Ketimine	Products (**6**–**17**)[24]	Yield %, (de)
1	**1a**	(*R*)-**3**	 (S_R,2*S*,5*R*,1′*R*)-**6** (S_R,2*S*,5*R*,1′*S*)-**7**	70, (66)
2	**1a**	(*R*)-**4**	 (S_R,2*S*,5*R*,1′*R*)-**8** (S_R,2*S*,5*R*,1′*S*)-**9**	74, (74)
3	**1a**	(*R*)-**5**	 (S_R,2*S*,5*R*,1′*R*)-**10** (S_R,2*S*,5*R*,1′*S*)-**11**	76, (82)
4	**2a**	(*R*)-**3**	 (S_R,2*S*,5*R*,1′*R*)-**12** (S_R,2*S*,5*R*,1′*S*)-**13**	55, (90)
5	**2a**	(*R*)-**4**	 (S_R,2*S*,5*R*,1′*R*)-**13** (S_R,2*S*,5*R*,1′*S*)-**14**	53, (84)
6	**2a**	(*R*)-**5**	 (S_R,2*S*,5*R*,1′*R*)-**16** (S_R,2*S*,5*R*,1′*S*)-**17**	52, (84)

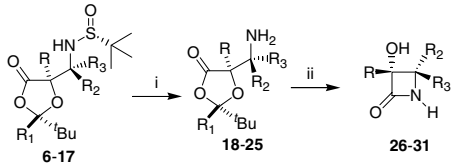
dioxolanones **18**–**25** in high yields. Diastereomeric excesses of the major (2*S*,5*R*,1′*R*)-diastereomers **18** and **20** were identical to those of their precursors **6/7** and **8/9**. LHMDS induced cyclization of the 1′aminodioxolanones **18**, **20**, and **22**–**25** produced 3-hydroxy-β-lactams (3*R*,4*R*)-**26**–**28** and (3*R*,4*S*)-**29**–**31**. Compounds (3*R*,4*R*)-**27** and (3*R*,4*R*)-**26** were obtained along with minor amounts of their (3*R*,4*S*)-isomers, but chromatography purification (SiO_2, CH_2Cl_2/Et_2O, 1:1) allowed their isolation. The relative stereochemical configuration of β-lactams **26**–**31** was assigned by means of ^1H NMR-NOE experiments. This allowed the assessment of stereoconfiguration at the 1′ position of their precursors **18**–**25** and **6**–**17**, hence of their absolute configuration.

With the aim of proving protecting group orthogonality (nitrogen atom and acetal center), we selectively transformed derivative (S_R,2*S*,5*R*,1′*R*)-**10** into the corresponding methyl ester (S_R,2*R*,3*R*)-**32**,[26] by base induced methanolysis (Scheme 2).

Access to sterically congested oligopeptides bearing two adjacent quaternary stereogenic centers was preliminarily explored by reacting 1′-amino-dioxolanone (2*S*,5*R*,1′*R*)-**22** with *N*,*N*-dimethylglycine (DMG). We reasoned that the dioxolanone protecting group would have favored the coupling reaction, because the 2-OH and the carboxy groups are 'tied back' in the form of a five-membered ring. Accordingly, the reduced steric hindrance would have allowed the use of milder coupling conditions. As reported in Scheme 3, the reaction was performed according to standard procedure. Namely, the diastereomeric mixture **20/21** was reacted with DMG in the presence of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride in a 3:1 (DMF/CH_2Cl_2) mixed solvent, yielding the fully protected dipeptide mixture **33/34** in 75% yield (74% de).

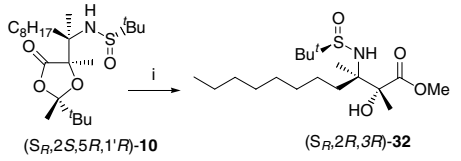
In conclusion, we reported the first synthesis of enantiopure *syn*/*anti* $\beta^{2,2,3,3}$-isoserines in the form of N,O-orthogonally protected 1′-amino-dioxolan-4-ones. Our synthetic protocol allows to achieve good values of overall yields and diastereoselectivities, overcoming the difficulties associated with the previously reported methodologies, such as the not easy differentiation between the two substituents on the prochiral ketimines

Table 2. Deprotection of compounds **6/7**, **8/9**, **10**, **13**, **15**, and **17** and synthesis of the corresponding β-lactams **26–31**[25]

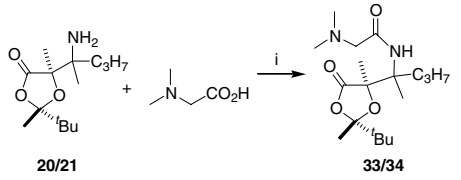


Entry	6–17	18–25[a] (de) Yield (%)	R, R_2, R_3	26–31[b] (de); Yield (%)
1	**6/7**[c]	**18/19**[c] (66); 90	Me, Me, C_2H_5	(3*R*,4*R*)-**26**[d] (50); 75
2	**8/9**[c]	**20/21**[c] (74); 90	Me, Me, C_3H_7	(3*R*,4*R*)-**27**[d] (55); 72
3	**10**[c]	**22**[c] (>98); 88	Me, Me, C_8H_{17}	(3*R*,4*R*)-**28** (>98); 74
4	**13**[d]	**23**[d] (>98); 88	C_6H_5, C_2H_5, Me	(3*R*,4*S*)-**29** (>98); 40
5	**15**[d]	**24**[d] (>98); 94	C_6H_5, C_3H_7, Me	(3*R*,4*S*)-**30** (>98); 35
6	**17**[d]	**25**[d] (>98); 98	C_6H_5, C_8H_{17}, Me	(3*R*,4*S*)-**31** (>98); 46

[a] 2 N HCl in MeOH/Et_2O.
[b] LHMDS/THF/HMPA.
[c] R_1 = Me.
[d] R_1 = H.



Scheme 2. Reagents and conditions: MeO^-/MeOH; 60 °C; 5 h; 86%.



Scheme 3. Reagents and conditions: EDC·HCl/HOBt/DMF:CH_2Cl_2, 3:1, 20 °C; 12 h; Y: 75%; de: 74%.

carbon atom and their low reactivity. The results achieved by us were possible primarily because of the high enolates stability, along with the high reactivity of the (*S*$_R$)-*N*-*tert*-butyl sulfinyl ketimines employed.

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20. General procedure for the synthesis of *N*-sulfinyl 1′-aminodioxolanones: LHMDS (2.8 equiv, 1.0 M in THF)

was added dropwise to a stirred THF solution of dioxolanone (2.8 equiv, 0,01 M) at −78 °C. The solution was reacted at −70 °C for further 45 min, then the temperature was lowered at −90 °C and HMPA was added dropwise (final THF/HMPA ratio, 85:15). After few minutes, the temperature was raised to −78 °C and a THF solution of the *N*-sulfinyl azomethine (1.0 equiv, 0.12 M) was slowly added. The temperature was raised to −60 °C during 1 h and then stirred for additional 30 min. The reaction mixture was quenched with 0.2 N HCl , warmed under stirring to room temperature, then extracted with EtOAc (3×), washed with 0.2 N HCl, followed by saturated NH_4Cl. The organic phase was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude material was purified by silica gel column chromatography; eluent: hexanes/ethyl acetate.

21. These results were confirmed in a test experiment of addition reaction of (2*S*)-**1a** with the (*S*)-configured ketimine (S_S)-**3**, which afforded modest amounts (30–35%) of a mixture of three diastereomers.
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23. Common feature of these reagents was the presence of the oxo group at the 2-position. Ketimines derived from isomeric ketones, such as hexan-3-one, or ketones bearing an aromatic substituent, such as acetophenone, were unreactive.
24. (S_R,2*S*,5*R*,1′*R*)-**10**: $[\alpha]_D^{20}$ −53 (*c* 0.5, $CHCl_3$). IR (neat, cm^{-1}) 2958, 1777, 1468. MS *m*/*z* 431, 327, 106. ^1H NMR ($CDCl_3$) δ 4.30 (b, 1H, NH), 1.86–1.76 (m, 1H), 1.68–1.62 (m, 2H), 1.61 (s, 3H, Me), 1.60 (s, 3H, Me), 1.47 (s, 3H, C1′-Me), 1.48–1.40 (m, 1H), 1.32–1.24 (m, 10H), 1.24 (s, 9H, S-^{t}Bu), 1.03 (s, 9H, 3 Me, C2-^{t}Bu), 0.88 (t, 3H, Me); ^{13}C NMR ($CDCl_3$) δ 175.1 (C), 115.7 (C), 84.8 (C), 62.3 (C), 56.5 (C), 39.5 (C), 37.1 (CH_2), 32.0 (CH_2), 30.5 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 25.8 (3 Me of S^{t}Bu), 24.5 (CH_2), 23.6 (Me), 23.3 (Me), 23.1 (3 Me of O^{t}Bu), 22.8 (CH_2), 22.3 (Me), 21.3 (Me),14.3 (Me). Anal. Calcd for $C_{23}H_{45}NO_4S$: C, 63.99; H, 10.51; N, 3.24. Found: C, 63.82; H, 10.72; N, 3.20.
25. (3*R*,4*R*)-**28**: $[\alpha]_D^{20}$ −4.6 (*c* 4.8, $CHCl_3$). IR (neat, cm^{-1}) 3248, 2925, 1773, 1468. MS *m*/*z* 227, 210, 114. ^1H NMR (CD_3COCD_3) δ 7.12 (b, 1H, NH), 4.72 (b, 1H, OH), 1.55–1.45 (m, 2H), 1.37 (s, 3H, C3-Me), 1.31 (s, 3H, C4-Me), 1.40–1.20 (m, 12H), 0.88 (t, 3H, Me); ^{13}C NMR (CD_3COCD_3) δ 171.6 (C), 84.6 (C), 63.0 (C), 37.1 (CH_2), 31.9 (CH_2), 30.3 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 25.1 (CH_2), 22.6 (CH_2), 20.1 (Me), 18.1 (Me), 13.7 (Me). Anal. Calcd for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; N, 6.16. Found: C, 68.56; H, 10.95; N, 6.28.
26. (S_R,2*R*,3*R*)-**32**: $[\alpha]_D^{20}$ +70.4 (*c* 0.75, $CHCl_3$). IR (neat, cm^{-1}) 3319, 2926, 2855, 1717, 1465. MS *m*/*z* 349, 332, 301, 227, 210, 179. ^1H NMR ($CDCl_3$) δ 4.53 (br s, 1 H, NH), 3.76 (s, 3H, CH_3), 1.86–1.76 (m, 1H), 1.41 (s, 3H, Me), 1.28 (s, 3H, Me), 1.27–1.22 (s+br m, 23 H , ^{t}Bu+7CH_2), 1.48–1.40 (m, 1H), 1.32–1.24 (m, 1H), 0.88 (t, 3H, Me); ^{13}C NMR ($CDCl_3$) δ 176.1 (C), 79.1, 64.9, 56.3 (C), 52.7 (CH_3), 38.7, 32.0 (CH_2), 31.1 (CH_3), 30.2, 29.8, 29.4, 23.8 23.2 (CH_3), 22.9 (CH_2), 21.1, 17.5, 14.3 (CH_3). Anal. Calcd for $C_{17}H_{35}NO_4S$: C, 58.42; H, 10.09; N, 4.01. Found: C, 58.31; H, 9.85; N, 4.27.