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Synthesis of chiral β^{2,2,3}-3-amino-2-hydroxyalkanoates and 3-alkyl-3-hydroxy-β-lactams by double asymmetric induction

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Abstract—Reactions of chiral (2*S*)-enolates of dioxolan-4-ones, derived from lactic, mandelic, and phenyllactic acids, with aliphatic (S_S)- and (S_R)-*tert*-butylsulfinyl aldimines afforded conformationally restrained C2-disubstituted *N*,*O*-orthogonally protected 3-amino-2-hydroxyalkanoates in the form of *N*-sulfinyl protected 1′-aminodioxolan-4-ones. The product distribution showed that there is significant kinetic selectivity, due to the presence of 'matched' and 'mismatched' components, between the (*S*)- or (*R*)-*tert*-butylsulfinyl aldimines and the (2*S*)-enolates of the 1,3-dioxolan-4-ones. Selective methoxide-induced removal of the acetal group of the *N*-sulfinyl-1′-aminodioxolanones yielded the corresponding *N*-sulfinyl protected methyl alkanoates. In addition, the selective acid-induced removal of the sulfinyl group of the *N*-sulfinyl-1′-aminodioxolanones provided the corresponding *N*-unprotected 1′-aminodioxolanones, whose base-induced cyclization afforded the corresponding β-lactams.

1. Introduction

3-Amino-2-hydroxyalkanoic acids find several applications in medicinal chemistry due to the presence of the hydroxyethylamine core structure, which mimics the tetrahedral transition state of peptidase amide bond hydrolysis.[1] This family of β-amino acids exhibits a per se inhibitory activity against aminopeptidase-2 (MetAP2), being useful for treating cancer conditions, which are exacerbated by angiogenesis.[2] Moreover, these compounds can serve as building blocks for the synthesis of oligopeptides, which are recognized as displaying inhibitory activity against several proteases, including renin,[3] HIV retropepsins,[4] plasmepsins,[5] cathepsins,[6] and pepsins[7] involved in important pathologies regarding blood pressure regulation such as HIV, malaria, and Alzheimer's disease. These β-amino acids are also employed as appendants for anti-neoplastic taxol analogs.[8]

Our contribution in this field concerns the synthesis of chiral α-hydroxy-β-amino acids, which are characterized by a conformational constraint due to the presence of an additional substituent at the C2 carbon atom.[9] The synthesis of constrained analogs of biologically active molecules is a widespread procedure to reduce the number of possible conformations. This practice was shown to be particularly attractive for peptide synthesis, whose number of solution conformations can be reduced by the presence of this additional substituent. As long as the biological activity is preserved, these less flexible analogs gain affinity toward the receptor, primarily for entropic reasons.[10] Moreover, the presence of a tertiary alcohol in the transition-state mimicking unit will possibly improve the membrane permeation properties and decrease the enzymatic hydrolysis.[11]

Our previous investigations have focused on the reaction between chiral enolates of 1,4-dioxolanones and *N*-BOC aromatic and heteroaromatic aldimines[12] and *C*-glycosylsulfinyl aldimines.[13] These reactions proved to be a powerful method for the synthesis of 1′-aminodioxolanones, which can be considered as orthogonally *N*,*O*-protected norstatines.

In continuing our studies on this subject, we considered the synthesis of α-hydroxy-β-aminoalkanoic acids, which are key scaffolds of many potent peptidomimetics. For this purpose, we selected activated aliphatic chiral *N*-*tert*-butylsulfinyl aldimines as the proper partners (Scheme 1), since they happen to be more stable compared to their BOC protected counterparts, which can only be generated in situ. However, the presence of a stereogenic center in the imine skeleton provides an additional element of kinetic selectivity with respect to the reactions performed with achiral *N*-BOC substituted counterparts. In addition to a full account of the synthetic results, we provide here a preliminary rationalization of the stereochemical outcome, based on all 'matching'

Keywords: Dioxolan-4-ones; Double asymmetric induction; Aldimines; α-Hydroxy-β-amino acids; 3-Hydroxy-β-lactams.
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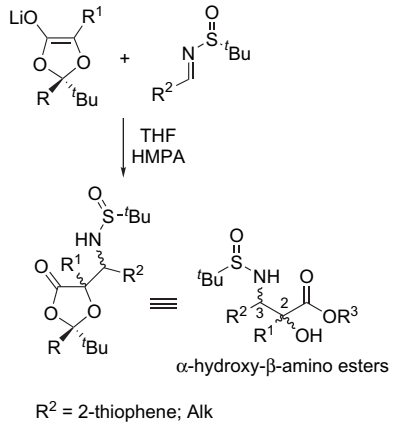
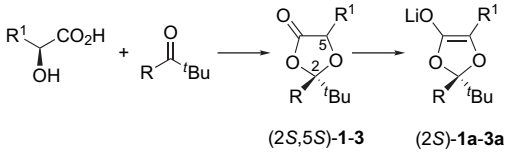
and 'mismatching' components. Qin and co-workers have very recently demonstrated the key role of sulfur chirality in terms of diastereoselectivity control in the addition of (*R*)-*tert*-butylsulfinyl amines to achiral enolates of *O*-BOC-α-hydroxy acetates.[14] Based on this report, we decided to evaluate the sulfur chirality effect on our product distribution, not only in reactions involving aliphatic sulfinyl imines but also in a reaction involving a heteroaromatic imine derived from thiophene-2-carbaldehyde.



Scheme 1. General scheme for the α-hydroxy-β-amino acid synthesis.

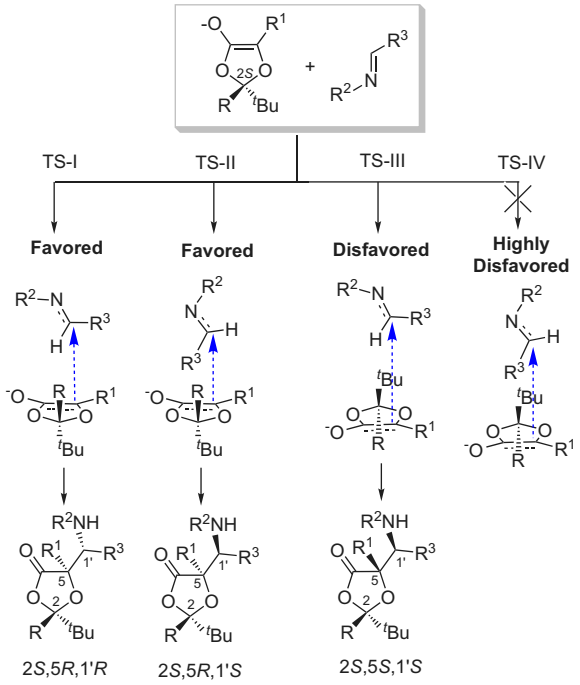
For this study, we selected the three 1,4-dioxolanones **1**–**3**, which are characterized by a different steric demand at both the C2 and C5-position, in order to evaluate their reactivity and stereochemical effect. These compounds are readily available from acetalization of chiral α-hydroxy acids with aldehydes or ketones.[15] In particular, we selected naturally occurring (2*S*)-lactic, benzyllactic and mandelic acids, which were reacted with pivaldehyde or pinacolone (Scheme 2).



1, **1a**: R=R^1= Me; **2**, **2a**: R= H; R^1= CH_2Ph; **3**, **3a**: R=H; R^1= Ph

Scheme 2.

The (2*S*,5*S*)-1,3-dioxolan-4-one major isomers were isolated as homochiral material, or in a very high diastereomeric excess, by re-crystallization (de>98%). Treatment of the dioxolanones with lithiated bases afforded the corresponding (2*S*)-chiral enolates **1a**–**3a**. As shown in Scheme 3, the addition of chiral (2*S*)-enolates to aliphatic aldimines can in principle give rise to the formation of four diastereoisomers, arising from the different approach of the enolate to the aldimine (transition states: TS-I, TS-II, TS-III, and TS-IV). The enantiomeric (2*R*)-enolates would provide their enantiomers. Since the (2*R*)-α-hydroxy acids can be readily obtained from the corresponding (2*R*)-α-amino acids, this feature is particularly useful in terms of biologically active analogs synthesis. The final product distribution will be the result of facial and simple selectivities. It is expected that the enolate will predominantly approach the aldimine from the less hindered diastereotopic face, so compounds arising from TS-I and TS-II will be favored, while TS-III and especially TS-IV will be highly disfavored because of the severe steric repulsion between R^3 and the *tert*-butyl group of the dioxolanone ring[9c] (Scheme 3). Besides, simple *exo*/*endo* selectivity will control the stereochemistry at the newly formed C1′ chiral center.



Scheme 3.

For our study the heteroaromatic aldimines[16] (*S*$_S$)-**4** and (*S*$_R$)-**4**, derived from thiophene-2-carbaldehyde, and the aliphatic *tert*-butylsulfinyl aldimines (*S*$_S$)-**5**–**7** and (*S*$_R$)-**5**–**7**, derived from isovaleraldehyde, 2-phenylacetaldehyde, and isobutyraldehyde, respectively, were employed (Fig. 1).

These aldehydes were selected on the basis of the potential biological activity of their resulting trisubstituted α-hydroxy-β-amino acids obtained by our enolate/aldimine protocol (Chart 1).

For example, α-hydroxy-β-amino acids bearing a heteroaromatic substituent at the C3-position, such as the 2-thienyl group, are found as side chains of potent antitumor taxanes.[11,17] The C2-methyl substituted analogs were obtained by reaction of the enolate **1a** with the 2-thienylaldimines (*S*$_S$)- and (*S*$_R$)-**4**.

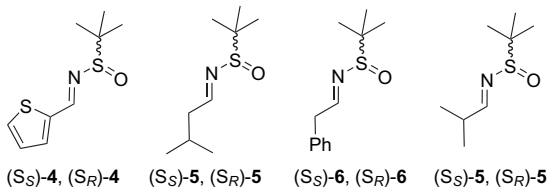


Figure 1.

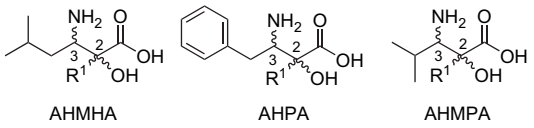


Chart 1. Scaffolds of the 3-amino-2-hydroxyalkanoic acid analogs.

The C2-analogs, which contain the aliphatic 3-amino-2-hydroxy-5-methylhexanoic [AHMHA] scaffold, were obtained by reaction of enolates **1a**–**3a** with isovaleraldimines (S_S)-**5** and (S_R)-**5**. The chiral [AHMHA] scaffold is contained in several aminopeptidases, such as amastatin,[18] leuhistin,[19] KRI-1230,[20] renin,[21] bombesin,[22] and apstatin.[23]

The C2-analogs, which contain the aliphatic 3-amino-2-hydroxy-4-phenylbutanoic acid [AHPA] scaffold, were obtained by reaction of enolates **1a**–**3a** with 2-phenylacetaldimines (S_S)-**6** and (S_R)-**6**. The AHPA scaffold is present with different configurations in many inhibitors, such as the BACE1 amyloid,[24] bestatin,[25,26] aminopeptidases P[27] and N,[28] and in some peptides, which exhibit enkephalinase inhibitory activity.[29] Moreover, AHPA-based scaffolds of different configurations serve for the design of antiviral drugs, which target retroviral polyproteins by human immunodeficiency virus protease (HIV PR) and other aspartyl proteases, such as in potent plasmepsin inhibitors of the KNI family[30,31] and the low molecular weight peptide (HIV PR) protease KI2.[32]

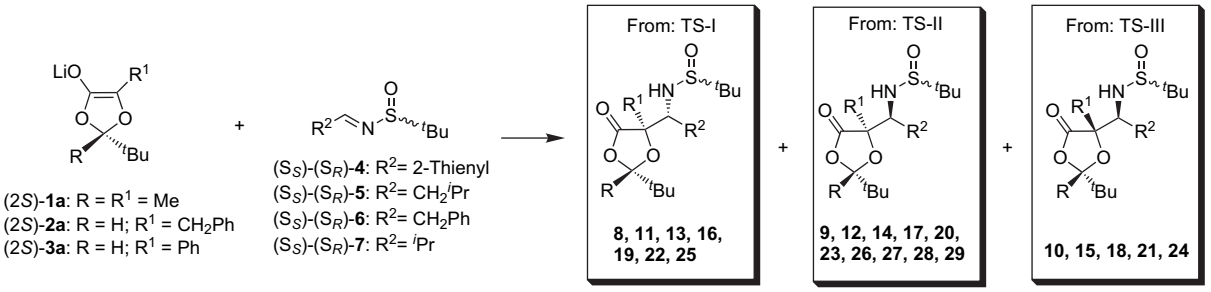
Finally, the analogs, which contain the 3-amino-2-hydroxy-4-methylpentanoic acid (AHMPA) scaffold, were obtained by reaction of **1a**–**3a** with isobutyraldimines (S_S)-**7** and (S_R)-**7**. This scaffold is found in lapstatin, a potent APN/CD13 inhibitor produced by *Streptomyces rimosus*.[33]

2. Results and discussion

2.1. Reactions of the (2*S*)-enolates 1a–3a with heteroaromatic sulfinyl imines (S_R)- and (S_S)-4 and aliphatic *N-tert*-butylsulfinyl azomethines (S_R)- and (S_S)-5–7

Table 1 shows the product distribution for the reactions between (S_R)- and (S_S)-sulfinyl aldimines **4**–**7** and (2*S*)-enolates **1a**–**3a**. In particular, entries 1–8 give the results arising from the reactions of the lithium enolate (2*S*)-**1a**. The major products of these reactions were the diastereomers derived from TS-I, regardless of the stereochemistry at the aldimine sulfur atom. In fact, the approach of the aldimine to the less hindered enantiotopic face of the enolate with the *C*-substituent *exo* to the dioxolanone ring was favored, due to the presence of the small methyl substituent at the C5 carbon atom. At the same time, the methyl group

Table 1. Addition of imines **4**–**7** to chiral enolates **1a**–**3a**



Entry	Enolate (R, R^1)	Imine[a] (R^2)	Isomers from [TS-I][a] (relative amount)	Isomers from [TS-II][a] (relative amount)	Isomer [TS-III][a] (relative amount)	Yield[b] (%)
1	(2*S*)-**1a** (R=R^1=Me)	(S_R)-**4** (2-Thienyl)	(S_R,2*S*,5*R*,1′*S*)-**8** (55.0)	(S_R,2*S*,5*R*,1′*R*)-**9** (45.0)	—	79
2	(2*S*)-**1a** (R=R^1=Me)	(S_S)-**4** (2-Thienyl)	(S_S,2*S*,5*R*,1′*S*)-**8** (80.0)	(S_S,2*S*,5*R*,1′*R*)-**9** (5.0)	(S_S,2*S*,5*S*,1′*R*)-**10** (15.0)	82
3	(2*S*)-**1a** (R=R^1=Me)	(S_R)-**5** ($CH_2{}^iPr$)	(S_R,2*S*,5*R*,1′*R*)-**11** (83.3)	(S_R,2*S*,5*R*,1′*S*)-**12** (16.7)	—	84
4	(2*S*)-**1a** (R=R^1=Me)	(S_S)-**5** ($CH_2{}^iPr$)	(S_S,2*S*,5*R*,1′*R*)-**11** (93.0)	(S_S,2*S*,5*R*,1′*S*)-**12** (7.0)	—	80
5	(2*S*)-**1a** (R=R^1=Me)	(S_R)-**6** (CH_2Ph)	(S_R,2*S*,5*R*,1′*R*)-**13** (63.0)	(S_R,2*S*,5*R*,1′*S*)-**14** (37.0)	—	78
6	(2*S*)-**1a** (R=R^1=Me)	(S_S)-**6** (CH_2Ph)	(S_S,2*S*,5*R*,1′*R*)-**13** (79)	—	(S_S,2*S*,5*S*,1′*S*)-**15** (21)	75
7	(2S)-**1a** (R=R^1=Me)	(S_R)-**7** (^iPr)	(S_R,2*S*,5*R*,1′*R*)-**16** (89.0)	(S_R,2*S*,5*R*,1′*S*)-**17** (9.0)	(S_R,2*S*,5*S*,1′*S*)-**18** (2.0)	88
8	(2S)-**1a** (R=R^1=Me)	(S_S)-**7** (^iPr)	(S_S,2*S*,5*R*,1′*R*)-**16** (≥98.0)	—	—	93
9	(2*S*)-**2a** (R=H, R^1=CH_2Ph)	(S_R)-**5** ($CH_2{}^iPr$)	(S_R,2*S*,5*R*,1′*R*)-**19** (24.0)	(S_R,2*S*,5*R*,1′*S*)-**20** (72.0)	(S_R,2*S*,5*S*,1′*S*)-**21** (4.0)	77
10	(2*S*)-**2a** (R=H, R^1=CH_2Ph)	(S_S)-**5** ($CH_2{}^iPr$)	(S_S,2*S*,5*R*,1′*R*)-**19** (45.7)	—	(S_S,2*S*,5*S*,1′*S*)-**21** (54.3)	79
11	(2*S*)-**2a** (R=H, R^1=CH_2Ph)	(S_R)-**6** (CH_2Ph)	(S_R,2*S*,5*R*,1′*R*)-**22** (45.0)	(S_R,2*S*,5*R*,1′*S*)-**23** (50.0)	(S_R,2*S*,5*S*,1′*S*)-24 (5.0)	58[c]
12	(2*S*)-**2a** (R=H, R^1=CH_2Ph)	(S_S)-**6** (CH_2Ph)	(S_S,2*S*,5*R*,1′*R*)-**22** (73.0)	—	(S_S,2*S*,5*S*,1′*S*)-**24** (27.0)	60
13	(2*S*)-**2a** (R=H, R^1=CH_2Ph)	(S_R)-**7** (^iPr)	(S_R,2*S*,5*R*,1′*R*)-**25** (56.5)	(S_R,2*S*,5*R*,1′*S*)-**26** (43.5)	—	61
14	(2*S*)-**2a** (R=H, R^1=CH_2Ph)	(S_S)-**7** (^iPr)	(S_S,2*S*,5*R*,1′*R*)-**25** (88.6)	(S_S,2*S*,5*R*,1′*S*)-**26** (11.4)	—	70
15	(2*S*)-**3a** (R=H, R^1=Ph)	(S_{SR})-**5** ($CH_2{}^iPr$)	—	(S_R,2*S*,5*R*,1′*S*)-**27**+ (S_S,2*S*,5*R*,1′*S*)-**27** (100.0)	—	86
16	(2*S*)-**3a** (R=H, R^1=Ph)	(S_{SR})-**6** (CH_2Ph)	—	(S_R,2*S*,5*R*,1′*S*)-**28**+ (S_S,2*S*,5*R*,1′*S*)-**28** (100.0)	—	75
17	(2*S*)-**3a** (R=H, R^1=Ph)	(S_S)-**7** (^iPr)	—	(S_S,2*S*,5*R*,1′*S*)-**29** (100.0)	—	80

[a] In the (S_R) or (S_S) terms for the *N-tert*-butylsulfinyl aldimines and *N-tert*-butylsulfinyl-1′-aminodioxolan-4-ones, the '*S*' and '*R*' in subscripts refer to the *S* or *R* chirality of the sulfur atom (S).

[b] Overall yields.

[c] Yield refers to a 60% aldimine conversion.

at the C2 acetal center inhibits the competitive approach of the aldimine according to TS-II, i.e., with the *C*-substituent *endo* to the ring. However, with respect to the (S_R)-aldimines, the (S_S)-configured aldimines favored the formation of diastereomers derived from TS-I, as appears by a comparison between entries 2, 4, 6, and 8 [where (S_S)-configured aldimines were employed] and entries 1, 3, 5, and 7 [which employed (S_R)-configured aldimines]. Sulfur chirality also affects the product distribution for compounds derived from TS-II and TS-III. Thus, the formation of isomers derived from TS-II is favored in reactions involving (S_R)-sulfinyl aldimines, while the stereoisomers derived from TS-III are strongly inhibited. For instance, the relative amounts of (S_R)-**9** (45.0), (S_R)-**12** (16.7), (S_R)-**14** (37.0), and (S_R)-**17** (9.0) are greater than those of the corresponding (S_S)-configured isomers, namely (S_S)-**9** (5.0), (S_S)-**12** (7.0), (S_S)-**14** (no formation), and (S_S)-**17** (no formation). Accordingly, the isomers derived from TS-III are only favored when (S_S)-sulfinyl aldimines are the partners, such as in the reactions of entries 2 and 6, which afforded consistent amounts of (S_S)-**10** (15.0) and (S_S)-**15** (21.0).

Entries 9–14 show the product distribution for the reactions of (2*S*)-**2a** with aldimines **5**–**7**. Enolate (2*S*)-**2a** differs from (2*S*)-**1a** by the presence of a smaller *H*-substituent at the C2 acetal center and a larger benzyl group at the C5 carbon atom. Accordingly, the *exo* approach of the aldimine to the dioxolanone ring is unfavorable, and thus a reduced formation of the (2*S*,5*R*,1′*R*)-diastereomers is observed. The sulfur chirality plays the same role already observed with enolate (2*S*)-**1a**, and thus aldimines (S_S)-**5**–**7** favor the formation of (2*S*,5*R*,1′*R*)-diastereomers (from TS-I) more than their (S_R)-**5**–**7** enantiomers. In addition, imines (S_R)-**5**–**7** more selectively form the (2*S*,5*R*,1′*S*)-isomers (S_R)-**20**, (S_R)-**23**, and (S_R)-**26** (entries 9, 11, and 13) from TS-II, while the (S_S)-**5** and (S_S)-**6** enantiomers favor the (2*S*,5*S*,1′*S*)-diastereomers (S_S)-**21** and (S_S)-**24** from TS-III. The effect of the sulfur atom stereochemistry can be explained by an unfavorable steric interaction between the sulfinyl substituents of (S_R)-configured aldimines in TS-III, which point toward the enolate ring. This interaction inhibits the formation of the (S_R,2*S*,5*S*,1′*S*)-sulfinylamino-dioxolanones (Fig. 2).

In entries 15–17 of Table 1 are given the product distributions for the reactions of (2*S*)-**3a** with aldimines **5**–**7**. The sterically demanding C5 phenyl substituent of this enolate plays a pivotal role in the diastereoselection, since only the (2*S*,5*R*,1′*S*)-enantiomers, derived from TS-II, were formed regardless of sulfur chirality. Aldimines **5** and **6** were used as racemic mixtures [(S_{SR})-**5** and (S_{SR})-**6**], while aldimine **7** was used as a pure (S_S)-enantiomer [(S_S)-**7**]. Accordingly, the racemic aldimines **5** and **6** afforded a mixture of (S_S,2*S*,5*R*,1′*S*)- and (S_R,2*S*,5*R*,1′*S*)-diastereomers

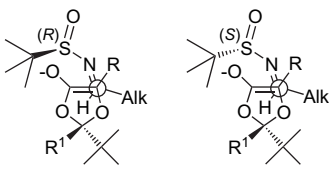


Figure 2.

[compounds (S_{SR})-**27** from (S_{SR})-**5**, and (S_{SR})-**28** from (S_{SR})-**6**], while the enantiomerically pure aldimine (S_S)-**7** provided (S_S)-**29** exclusively.

2.2. Selective deprotection of the *N*-*tert*-butylsulfinyl-1′-aminodioxolanone moiety and stereoconfigurational assessment

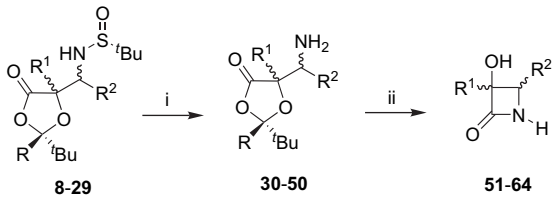
In order to prove the orthogonality between the acetal and sulfinyl protecting groups, the *N*-*tert*-butylsulfinylamino group of 1′-aminodioxolanones **8**–**29** was selectively removed by ethereal HCl treatment, affording the corresponding free amines **30**–**50** in very good yields. This deprotection reaction allowed the subsequent synthesis of chiral 3-substituted 3-hydroxy-2-azetidinones, via base-induced cyclization of the corresponding free amines. These compounds represent an efficient carboxylate mimic,[34] being present in several pharmacologically active monobactams, such as sulfazecin and related products,[35] and in enzyme inhibitors such as tabtoxin and its analogs.[36] In addition, the synthesis of the β-lactams provided an entry to the absolute stereochemistry assignment at the 1′-position of the *N*-*tert*-butylsulfinyl-1′-aminodioxolanones. In particular, the LHMDS-induced cyclization of free amines **30**–**50** provided the corresponding β-lactams **51**–**64**, whose C4 stereochemistry, which corresponds to that of the C1′ carbon atom of the parent 1′-aminodioxolanones, was assessed by means of NOE experiments (see Table 2 and Section 4 for details). On the other hand, the stereochemistry at the C5-position was assigned by means of NOE experiments, performed either on the 1′-sulfinylamino-dioxolanones or on their free amines. The orthogonality of the *N*-sulfinyl and the acetal protecting groups was demonstrated by performing selective acetal removal on compounds (S_R)-**13**, (S_S)-**16**, (S_S)-**21**, and (S_S)-**29**, by base-induced methanolysis, which afforded the corresponding *N*-*tert*-butylsulfinyl protected α-hydroxy-β-amino methyl esters (S_R,2*R*,3*R*)-**65**, (S_S,2*R*,3*R*)-**66**, (S_S,2*S*,3*S*)-**67**, and (S_S,25*R*,3*S*)-**68**, respectively, in good yields (Table 3).

3. Conclusions

We have described here a versatile and general method for the synthesis of enantiopure conformationally restrained C2-disubstituted 3-amino-2-hydroxyalkanoates and sterically congested trisubstituted 3-alkyl-3-hydroxy-β-lactams. Both classes of compounds are very important building blocks in medicinal chemistry. Moreover, the amino acids are obtained in the form of *N*,*O*-orthogonally protected 1′-aminodioxolan-4-ones.

This methodology allows the insertion of bulky substituents, such as the phenyl group, at the C2 carbon atom of the amino acid and/or the corresponding β-lactam. These targets are difficult to synthesize by other methodologies. Moreover, it is possible to control, or at least to reduce, the number of possible diastereomers since the formation of products derived from TS-IV is precluded due to a severe repulsion between the *tert*-butyl substituent of the enolate and that at the carbon atom of the aldimines. Besides, the formation of epimers derived from TS-III is almost suppressed by using (S_R)-configured *N*-*tert*-butylsulfinyl aldimines.

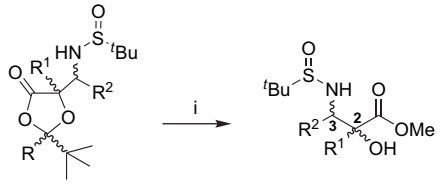
Table 2. Deprotection of S_S- and S_R-*N*-*tert*-butylsulfinyl-1′-aminodioxolanones **8–29**, affording the corresponding 1′-aminodioxolanones **30–50**, and synthesis of the corresponding β-lactams **51–64**[a]



Entry	R	R^1	R^2	**8–29**	**30–50** (Yield, %)	**51–64** (Yield[b], %)
1	Me	Me	2-Thienyl	(*S*$_S$,2*S*,5*R*,1′*S*)-**8**	(2*S*,5*R*,1′*S*)-**30** (82)	(3*R*,4*S*)-**51** (82)
				(*S*$_R$,2*S*,5*R*,1′*S*)-**8**	(2*S*,5*R*,1′*S*)-**30** (82)	
2	Me	Me	2-Thienyl	(*S*$_R$,2*S*,5*R*,1′*R*)-**9**	(2*S*,5*R*,1′*R*)-**31** (86)	(3*R*,4*R*)-**52** (82)
				(*S*$_S$,2*S*,5*R*,1′*R*)-**9**	(2*S*,5*R*,1′*R*)-**31**	
4	Me	Me	$CH_2{}^iPr$	(*S*$_S$,2*S*,5*R*,1′*R*)-**11**	(2*S*,5*R*,1′*R*)-**35** (73)	(3*R*,4*R*)-**53** (82)
				(*S*$_R$,2*S*,5*R*,1′*R*)-**11**	(2*S*,5*R*,1′*R*)-**35** (83)	
5	Me	Me	$CH_2{}^iPr$	(*S*$_S$,2*S*,5*R*,1′*S*)-**12**	(2*S*,5*R*,1′*S*)-**36** (86)	(3*R*,4*S*)-**54** (78)
				(*S*$_R$,2*S*,5*R*,1′*R*)-**12**	(2*S*,5*R*,1′*S*)-**36** (80)	
6	Me	Me	CH_2Ph	(*S*$_R$,2*S*,5*R*,1′*R*)-**13**	(2*S*,5*R*,1′*R*)-**37** (91)	(3*R*,4*R*)-**55** (82)
				(*S*$_s$,2*S*,5*R*,1′*R*)-**13**	(2*S*,5*R*,1′*R*)-**37** (88)	
7	Me	Me	CH_2Ph	(*S*$_R$,2*S*,5*R*,1′*S*)-**14**	(2*S*,5*R*,1′*S*)-**38** (85)	—
8	Me	Me	CH_2Ph	(*S*$_S$,2*S*,5*S*,1′*S*)-**15**	(2*S*,5*S*,1′*S*)-**39** (88)	—
9	Me	Me	^iPr	(*S*$_S$,2*S*,5*R*,1′*R*)-**16**	(2*S*,5*R*,1′*R*)-**40** (85)	(3*R*,4*R*)-**56** (87)
				(*S*$_R$,2*S*,5*R*,1′*R*)-**16**	(2*S*,5*R*,1′*R*)-**40** (81)	
10	H	CH_2Ph	$CH_2{}^iPr$	(*S*$_S$,2*S*,5*R*,1′*R*)-**19**	(2*S*,5*R*,1′*R*)-**41** (91)	(3*R*,4*R*)-**57** (85)
				(*S*$_R$,2*S*,5*R*,1′*R*)-**19**	(2*S*,5*R*,1′*R*)-**41** (82)	
11	H	CH_2Ph	$CH_2{}^iPr$	(*S*$_R$,2*S*,5*R*,1′*S*)-**20**	(2*S*,5*R*,1′*S*)-**42** (85)	—
12	H	CH_2Ph	$CH_2{}^iPr$	(*S*$_S$,2*S*,5*S*,1′*S*)-**21**	(2*S*,5*S*,1′*S*)-**43** (82)	(3*S*,4*S*)-**58** (78)
13	H	CH_2Ph	CH_2Ph	(*S*$_R$,2*S*,5*R*,1′*R*)-**22**	(2*S*,5*R*,1′*R*)-**44** (90)	(3*R*,4*R*)-**59** (88)
				(*S*$_S$,2*S*,5*R*,1′*R*)-**22**	(2*S*,5*R*,1′*R*)-**44** (88)	
14	H	CH_2Ph	CH_2Ph	(*S*$_S$,2*S*,5*S*,1′*S*)-**24**	(2*S*,5*S*,1′*S*)-**45** (83)	(3*S*,4*S*)-**60** (81)
15	H	CH_2Ph	^iPr	(*S*$_S$,2*S*,5*R*,1′*R*)-**25**	(2*S*,5*R*,1′*R*)-**46** (88)	(3*R*,4*R*)-**61** (87)
				(*S*$_R$,2*S*,5*R*,1′*R*)-**25**	(2*S*,5*R*,1′*R*)-**46**	
16	H	CH_2Ph	^iPr	(*S*$_R$,2*S*,5*R*,1′*S*)-**26**	(2*S*,5*R*,1′*S*)-**47** (90)	
				(*S*$_S$,2*S*,5*R*,1′*S*)-**26**	(2*S*,5*R*,1′*S*)-**47**	
17	H	Ph	$CH_2{}^iPr$	(*S*$_R$,2*S*,5*R*,1′*S*)-**27**	(2*S*,5*R*,1′*S*)-**48** (92)	(3*R*,4*S*)-**62** (90)
				(*S*$_S$,2*S*,5*R*,1′*S*)-**27**		
18	H	Ph	CH_2Ph	(*S*$_R$,2*S*,5*R*,1′*S*)-**28**	(2*S*,5*R*,1′*S*)-**49** (72)	(3*R*,4*S*)-**63** (71)
				(*S*$_S$,2*S*,5*R*,1′*S*)-**28**		
19	H	Ph	^iPr	(*S*$_S$,2*S*,5*R*,1′*S*)-**29**	(2*S*,5*R*,1′*S*)-**50** (84)	(3*R*,4*S*)-**64** (88)

[a] Reagents and conditions: (i) 2 N HCl in 1/1 MeOH/Et_2O; (ii) LHMDS/THF/HMPA.
[b] Isolated yields.

Table 3. Synthesis of *N*-*tert*-butylsulfinyl protected α-hydroxy-β-amino methyl esters



Entry	R^1	R^2	Substrate[a]	Product	Yield[b] (%)
1	Me	CH_2Ph	(*S*$_R$,2*S*,5*R*,1′*R*)-**13**	(*S*$_R$,2*R*,3*R*)-**65**	75
2	Me	^iPr	(*S*$_S$,2*S*,5*R*,1′*R*)-**16**	(*S*$_S$,2*R*,3*R*)-**66**	90
3	CH_2Ph	$CH_2{}^iPr$	(*S*$_S$,2*S*,5*S*,1′*S*)-**21**	(*S*$_S$,2*S*,3*S*)-**67**	83
4	Ph	^iPr	(*S*$_S$,2*S*,5*R*,1′*S*)-**29**	(*S*$_S$,2*R*,3*S*)-**68**	87

[a] Reagents and conditions: (i) MeO^-/MeOH.
[b] Isolated yields.

4. Experimental

4.1. General experimental conditions

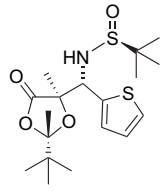
All reactions were performed under an atmosphere of dry nitrogen using oven-dried glassware. Tetrahydrofuran, toluene, and ethyl ether were distilled from sodium benzophenone ketal. Dichloromethane, HMPA, and acetonitrile were distilled from calcium hydride. All other solvents were of HPLC grade. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with E. Merck silica gel 60-F254 plates. Flash column chromatography was performed with Merck silica gel (0.04–0.63 μm, 240–400 mesh) under high pressure. NMR spectra were recorded on 400 MHz spectrometer. Unless otherwise stated, all NMR spectra were measured in $CDCl_3$ solutions and referenced to the $CHCl_3$ signal. All ^1H and ^{13}C shifts are given in parts per million (s=singlet; d=doublet; t=triplet; dd=quadruplet; dt=doublet of triplets, m=multiplet; br s=broad singlet). Coupling constants *J* are given in hertz. Assignments of proton resonances were confirmed, when possible, by selective homonuclear decoupling experiments

or by correlated spectroscopy. IR spectra were recorded on a FTIR E.S.P. spectrometer as thin films on NaCl plates. Mass spectra were recorded on an ion trap spectrometer with an ionization potential of 70 eV. High-resolution mass spectra (HRMS) were performed with a resolution of 10,000 against a suitable mass standard. The commercially available reagents were used as received without further purification. The *tert*-butylsulfinyl aldimines **4–7** were prepared from the corresponding aldehydes and chiral or racemic *tert*-butanesulfinamides[35] according to a literature method.[37] Dioxolanones (2*S*,5*S*)-**1–3** were prepared from the corresponding (*S*)-α-hydroxy acids according to a literature method.[15]

4.2. General procedure for the synthesis of *N*-sulfinyl-1′-aminodioxolanones

Unless otherwise stated, a THF solution of dioxolanone (2.0 mL of THF×0.25 g of dioxolanone, 2.8 equiv) was added dropwise at −78 °C to a solution of LHMDS in THF (2.8 equiv, 1.0 M). The solution was stirred at −70 °C for 30 min, then the temperature was lowered at −90 °C, and a THF solution of HMPA was added (final ratio THF/HMPA, 85/15). The temperature was raised to −78 °C and after 2 min, a THF solution of *N*-sulfinyl azomethine (1.0 equiv) was slowly added. After complete addition, the temperature was raised to −60 °C during 1 h and stirred at this temperature for additional 30 min. The reaction was quenched with 1.0 N HCl and warmed under stirring to room temperature. The reaction mixture was extracted with EtOAc (3×15 mL) and then washed three times with 0.2 N HCl followed by saturated NH_4Cl (2×10 mL). The organic phase was dried over Na_2SO_4 and after filtration the solvent was removed under vacuum. The mixture of diastereomers was purified, or separated when possible, by silica gel flash chromatography. A slightly modified procedure was adopted for the synthesis of the enolate (2*S*)-**2a**. Namely, 4.0 mL of THF×0.25 g of dioxolanone were slowly added at −85/−80 °C in 30 min to a solution of LHMDS in THF (2.8 equiv, 1.0 M). Subsequently, a THF solution of HMPA was very slowly added (20 min) at this temperature. The THF solution of the imine was also added at this temperature in 20 min. The reaction was quenched with 1.0 N HCl and warmed under stirring to room temperature and then worked up as already reported above. The crude material was purified by silica gel flash column chromatography.

4.2.1. Synthesis of (*S*$_S$,2*S*,5*R*,1′*S*)-8, (*S*$_S$,2*S*,5*R*,1′*R*)-9, and (*S*$_S$,2*S*,5*S*,1′*R*)-10. The dioxolanone (2*S*,5*S*)-**1** (420 mg, 2.44 mmol) was reacted with imine (*S*$_S$)-**4** (200 mg, 0.929 mmol). The ^{1}H NMR analysis of the crude mixture showed a product distribution of (*S*$_S$)-**8**/(*S*$_S$)-**9**/(*S*$_S$)-**10**= 16.0/1.0/3.0. Chromatography (SiO_2, *n*-hexane/Et_2O, 1/1), afforded compounds (*S*$_S$)-**8** (236 mg, 0.61 mmol, 65.7%), (*S*$_S$)-**10** (44 mg, 0.114 mmol, 12.3%), and (*S*$_S$)-**9** contaminated by trace amounts of impurities (15 mg, 0.0381 mmol, 4%) as pale oils. (*S*$_S$,2*S*,5*R*,1′*S*)-**8**: $[\alpha]_D^{20}$ +100.0 (*c* 0.43, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3270, 3200–3050, 1776; mp 161 °C; MS *m*/*z* 387, 282, 267, 215; ^{1}H NMR ($CDCl_3$) δ 7.28–7.24 (m, 1H, arom), 7.19–7.16 (m, 1H, arom), 7.02–6.97 (m, 1H, arom), 4.94 (d, 1H, *J*=4.2 Hz, H-1′), 4.19 (d, 1H, NH), 1.47 (s, 3H, Me), 1.26 (s, 3H, Me), 1.24 (s, 9H, 3Me), 0.98 (s, 9H, 3Me); ^{13}C NMR ($CDCl_3$) δ 173.4, 140.7, 127.6, 126.8, 125.8, 115.7, 82.0, 59.9, 57.4, 38.9, 24.8, 22.5, 22.4, 20.3. Anal. Calcd for $C_{18}H_{29}NO_4S_2$: C, 55.78; H, 7.54; N, 3.61. Found: C, 55.64; H, 7.66; N, 3.57. (*S*$_S$,2*S*,5*R*,1′*R*)-**9**: IR ($CDCl_3$, cm^{-1}) 3200–3050, 1771; HRMS *m*/*z* calcd for $C_{18}H_{29}NO_4S_2$ $[M]^+$: 387.1538, *m*/*z* found: 387.1533; ^{1}H NMR ($CDCl_3$) δ 7.26–7.22 (m, 1H, arom), 7.02–9.95 (m, 2H, arom), 5.12 (d, 1H, *J*=1.5 Hz, H-1′), 5.04 (d, 1H, *J*=1.0 Hz, NH), 1.71 (s, 3H, Me), 1.34 (s, 3H, Me), 0.96 (s, 9H, 3Me), 0.70 (s, 9H, 3Me); ^{13}C NMR ($CDCl_3$) δ 173.2, 142.1, 128.0, 127.1, 125.3, 116.8, 84.9, 60.9, 60.1, 39.2, 25.4, 24.2, 22.8, 21.9. The (5*R*)-stereoconfiguration of (*S*$_S$)-**9** was assigned by homonuclear NOE experiments ($CDCl_3$). Upon irradiation of the acetal *tert*-butyl group at 0.70 ppm, significant NOE effects (3.2 and 5.5%) were observed on the CH_3 protons at 1.71 and 1.34 ppm, respectively.

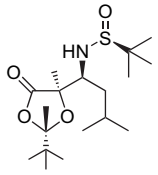


(S$_S$, 2*S*, 5*R*, 1′*R*)-**9**

(*S*$_S$,2*S*,5*S*,1′*R*)-**10**: $[\alpha]_D^{20}$ +76.0 (*c* 0.37, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3260, 3200–3050, 1778; mp 123–125 °C; MS *m*/*z* 387, 282, 267, 215; ^{1}H NMR ($CDCl_3$) δ 7.36–7.31 (m, 1H, arom), 7.16–7.11 (m, 1H, arom), 7.07–7.01 (m, 1H, arom), 5.20 (s, 1H, NH), 5.04 (s, 1H, H-1′), 1.55 (s, 3H, Me), 1.53 (s, 3H, Me), 1.30 (s, 9H, 3Me), 1.08 (s, 9H, 3Me); ^{13}C NMR ($CDCl_3$) δ 175.3, 137.4, 128.5, 126.5, 126.1, 116.4, 78.8, 56.9, 56.0, 38.7, 24.9, 22.8, 22.7, 19.4. Anal. Calcd for $C_{18}H_{29}NO_4S_2$: C, 55.78; H, 7.54; N, 3.61. Found: C, 55.91; H, 7.47; N, 3.66.

4.2.2. Synthesis of (*S*$_R$,2*S*,5*R*,1′*S*)-8 and (*S*$_R$,2*S*,5*R*,1′*R*)-9. The reaction of dioxolanone (2*S*,5*S*)-**1** (300 mg, 1.74 mmol) and imine (*S*$_R$)-**4** (136 mg, 0.63 mmol) afforded a 1.2/1 mixture of (*S*$_R$)-**8**/(*S*$_R$)-**9**. Silica gel column chromatography purification (*n*-hexane/Et_2O, 2/3) afforded compounds (*S*$_R$)-**8** (105 mg, 0.27 mmol, 43%) and (*S*$_R$)-**9** (87 mg, 0.22 mmol, 36%) as pale yellow oils. (*S*$_R$,2*S*,5*R*,1′*S*)-**8**: $[\alpha]_D^{20}$ −62.0 (*c* 0.46, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3270, 3200–3050, 1777; mp 107 °C; MS *m*/*z* 387, 282, 267, 215; ^{1}H NMR ($CDCl_3$) δ 7.32–7.28 (m, 1H, arom), 7.07–6.97 (m, 2H, arom), 5.00 (d, 1H, *J*=1.5 Hz, NH), 4.81 (d, 1H, H-1′), 1.57 (s, 3H, Me), 1.47 (s, 3H, Me), 1.28 (s, 9H, 3Me), 0.96 (s, 9H, 3Me); ^{13}C NMR ($CDCl_3$) δ 175.0, 138.6, 128.4, 126.9, 126.1, 116.6, 80.5, 58.5, 56.4, 39.0, 24.9, 23.4, 22.9, 18.9. Anal. Calcd per $C_{18}H_{29}NO_4S_2$: C, 55.78; H, 7.54; N, 3.61. Found: C, 55.91; H, 7.58; N, 3.55. (*S*$_R$,2*S*,5*R*,1′*R*)-**9**: $[\alpha]_D^{20}$ −5.0 (*c* 0.42, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3265, 3200–3050, 1776; mp 177 °C; MS *m*/*z* 387, 282, 267, 215; ^{1}H NMR ($CDCl_3$) δ 7.29–7.24 (m, 1H, arom), 7.20–7.14 (m, 1H, arom), 7.00–6.94 (m, 1H, arom), 4.79 (d, 1H, *J*=8.5 Hz, NH), 3.33 (d, 1H, H-1′), 1.66 (s, 3H, Me), 1.42 (s, 3H, Me), 1.19 (s, 9H, 3Me), 1.04 (s, 9H, 3Me); ^{13}C NMR ($CDCl_3$) δ 173.6, 140.2, 133.9, 128.3, 127.1, 115.9, 84.0, 62.5, 56.9, 39.2, 25.4, 23.4, 23.2, 22.7. Anal. Calcd for $C_{18}H_{29}NO_4S_2$: C, 55.78; H, 7.54; N, 3.61. Found: C, 55.85; H, 7.67; N, 3.68.

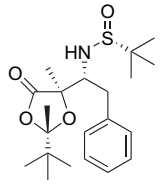
4.2.3. Synthesis of (S_S,2*S*,5*R*,1′*R*)-11 and (S_S,2*S*,5*R*,1′*S*)-12. The reaction of dioxolanone (2*S*,5*S*)-**1** (328 mg, 1.90 mmol) and imine (S_S)-**5** (128 mg, 0.676 mmol) afforded a 15.0/1.0 mixture of (S_S,2*S*,5*R*,1′*R*)-**11**/(S_S,2*S*,5*R*,1′*S*)-**12**. Silica gel purification (*n*-hexane/EtOAc, 2/1) afforded compounds (S_S)-**11** (184 mg, 0.51 mmol, 75%, sticky oil), and (S_S)-**12** (12 mg, 0.033 mmol, 5%, sticky oil). (S_S,2*S*,5*R*,1′*R*)-**11**: $[\alpha]_D^{20}$ +76.0 (*c* 0.43, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3492, 3126, 2963, 1792; mp 132 °C; MS *m*/*z* 361, 258, 177, 116, 87; ^1H NMR ($CDCl_3$) δ 3.57–3.48 (m, 1H, J_1=2.0 Hz, J_2=6.0 Hz, J_3=8.5 Hz, H-1′), 3.23 (d, 1H, *J*=3.2 Hz, NH), 2.02–1.92 (m, 1H, Me_2CH), 1.54 (s, 3H, Me), 1.43 (s, 3H, Me), 1.60–1.46 (m, 2H, CH_2), 1.26 (s, 9H, 3Me), 0.99 (s, 9H, 3Me), 0.97 (d, 3H, *J*=3.4 Hz, Me), 0.94 (d, 3H, Me); ^{13}C NMR ($CDCl_3$) δ 173.9, 114.3, 80.9, 59.3, 56.9, 39.6, 39.2, 24.9, 24.1, 23.5, 23.4, 23.1, 21.2, 18.2. Anal. Calcd for $C_{18}H_{35}NO_4S$: C, 59.80; H, 9.76; N, 3.87. Found: C, 59.67; H, 9.68; N, 3.94. (S_S,2*S*,5*R*,1′*S*)-**12**: $[\alpha]_D^{20}$ +49.0 (*c* 0.4, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3492, 3126, 2963, 1792; MS *m*/*z* 361, 258, 177, 116, 87; ^1H NMR ($CDCl_3$) δ 3.66 (d, 1H, *J*=5.4 Hz, NH), 3.57 (m, 1H, J_1=2.1 Hz, J_2=5.5 Hz, J_3=9.5 Hz, H-1′), 1.94–1.85 (m, 1H, Me_2CH), 1.64 (s, 3H, Me), 1.74 (m, 1H, CH_2), 1.43 (s, 3H, Me), 1.38 (m, 1H, CH_2), 1.23 (s, 9H, 3Me), 1.01 (s, 9H, 3Me), 0.95 (d, 3H, *J*=6.5 Hz, Me), 0.88 (d, 3H, *J*=6.5 Hz, Me). ^{13}C NMR ($CDCl_3$) δ 173.6, 115.1, 81.5, 58.6, 56.7, 40.0, 39.2, 25.4, 25.0, 24.0, 23.4, 22.9, 21.2, 18.1. Anal. Calcd for $C_{18}H_{35}NO_4S$: C, 59.80; H, 9.76; N, 3.87. Found: C, 59.72; H, 9.79; N, 3.76. The (5*R*)-configuration of (S_S,2*S*,5*R*,1′*S*)-**12** was assigned by NOE experiments ($CDCl_3$). Irradiation of the *tert*-butyl group at 1.01 ppm produced significant NOE effects (9.2 and 5.1%) on the methyl groups at C2 (1.64 ppm) and C5 (1.43 ppm), respectively.



(S_S, 2*S*, 5*R*, 1′*S*)-**12**

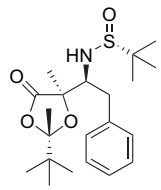
4.2.4. Synthesis of (S_R,2*S*,5*R*,1′*R*)-11 and (S_R,2*S*,5*R*,1′*S*)-12. The reaction of dioxolanone (2*S*,5*S*)-**1** (386 mg, 2.24 mmol) and imine (S_R)-**5** (151 mg, 0.80 mmol) afforded a 5/1 mixture of (S_R,2*S*,5*R*,1′*R*)-**11** and (S_R,2*S*,5*R*,1′*S*)-**12**. Silica gel purification (*n*-hexane/EtOAc, 2/1) provided compounds (S_R)-**11** (201 mg, 0.56 mmol, 70%), and (S_R)-**12** (42 mg, 0.12 mmol, 14%) as sticky oils. (S_R,2*S*,5*R*,1′*R*)-**11**: $[\alpha]_D^{20}$ −65.0 (*c* 0.4, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3220, 2960, 1777; MS *m*/*z* 361, 258, 177, 116, 87; ^1H NMR ($CDCl_3$) δ 4.30 (d, 1H, *J*=1.5 Hz, NH), 3.56–3.48 (m, 1H, H-1′), 2.01–1.83 (m, 1H, Me_2CH), 1.57–1.50 (m, 1H, CH_2), 1.52 (s, 3H, Me), 1.48–1.42 (m, 1H, CH_2), 1.43 (s, 3H, Me), 1.22 (s, 9H, 3Me), 0.97 (s, 9H, 3Me), 0.94 (d, 3H, *J*=3.4 Hz, Me), 0.90 (d, 3H, Me); ^{13}C NMR ($CDCl_3$) δ 175.1, 115.7, 81.0, 56.8, 56.3, 40.0, 39.0, 25.7, 25.0, 23.8, 23.5, 22.9, 22.1, 19.1. Anal. Calcd for $C_{18}H_{35}NO_4S$: C, 59.80; H, 9.76; N, 3.87. Found: C, 59.61; H, 9.65; N, 3.94. (S_R,2*S*,5*R*,1′*R*)-**12**: $[\alpha]_D^{20}$ −25.0 (*c* 0.54, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3220, 2960, 1776; mp 95 °C; MS *m*/*z* 361, 258, 177, 116, 87; ^1H NMR ($CDCl_3$) δ 3.56–3.48 (m, 1H, H-1′), 2.82 (d, 1H, *J*=3.2 Hz, NH), 2.04–1.88 (m, 1H, Me_2CH), 1.68–1.58 (m, 1H, CH_2), 1.61 (s, 3H, Me), 1.41 (s, 3H, Me), 1.36–1.26 (m, 1H, CH_2), 1.23 (s, 9H, 3Me), 0.99 (s, 9H, 3Me), 0.96 (d, 3H, *J*=6.4 Hz, Me), 0.93 (d, 3H, *J*=6.4 Hz, Me); ^{13}C NMR ($CDCl_3$) δ 172.4, 114.8, 83.5, 60.7, 56.7, 40.2, 39.1, 25.0, 24.1, 23.5, 23.2, 22.9, 21.1, 20.26. Anal. Calcd for $C_{18}H_{35}NO_4S$: C, 59.80; H, 9.76; N, 3.87. Found: C, 59.95; H, 9.83; N, 3.85.

4.2.5. Synthesis of (S_R,2*S*,5*R*,1′*R*)-13 and (S_R,2*S*,5*R*,1′*S*)-14. The reaction of dioxolanone (2*S*,5*S*)-**1** (0.45 g, 2.61 mmol) with aldimine (S_R)-**6** (208 mg, 0.93 mmol) afforded a 1.6/1.0 mixture of (S_R)-**13**/(S_R)-**14**. Silica gel chromatographic purification (*n*-hexane/Et_2O, 1.5/1) provided compounds (S_R)-**13** (0.18 g, 0.45 mmol, 48%) and (S_R)-**14** (0.11 g, 0.28 mmol, 30%) as vitreous oils. (S_R,2*S*,5*R*,1′*R*)-**13**: $[\alpha]_D^{20}$ −63.0 (*c* 0.84, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 2957, 1771, 1290, 1154; MS *m*/*z* 395, 193, 131, 91; ^1H NMR ($CDCl_3$) δ 7.28–7.16 (m, 5H, arom), 4.29 (d, 1H, NH), 3.87 (m, 1H, J_1=1.5 Hz, J_2=5.8 Hz, J_3=9.4 Hz, H-1′), 3.01 (m, 2H, CH_2–Ph), 1.57 (s, 3H, Me), 1.32 (s, 3H, Me), 1.15 (s, 9H, 3Me), 0.95 (s, 9H, 3Me); ^{13}C NMR ($CDCl_3$) δ 175.1, 138.6, 130.0, 128.5, 126.6, 116.1, 81.0, 60.6, 56.2, 39.0, 37.0, 25.0, 22.9, 22.8, 19.4. Anal. Calcd for $C_{21}H_{33}NO_4S$: C, 63.76; H, 8.41; N, 3.54. Found: C, 63.81; H, 8.47; N, 3.60. The (5*R*)-configuration of (S_R)-**13** was assigned by homonuclear NOE experiments ($CDCl_3$). Upon irradiation of the acetal *tert*-butyl group at 0.95 ppm, relevant NOE effects (5 and 6%) were observed on the methyl protons at 1.57 and 1.32 ppm, respectively.



(S_R, 2*S*, 5*R*, 1′*R*)-**13**

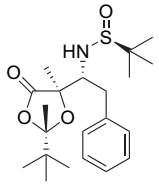
(S_R,2*S*,5*R*,1′*S*)-**14**: $[\alpha]_D^{20}$ −8.0 (*c* 0.50, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 2964, 1783, 1152; MS *m*/*z* 395, 193, 131, 91; ^1H NMR ($CDCl_3$) δ 7.32–7.22 (m, 5H, arom), 3.84 (m, 1H, H-1′), 3.35 (dd, 1H, J_1=5.5 Hz, J_2=14.5 Hz, CH_2–Ph), 3.33 (d, 1H, *J*=5.2 Hz, NH), 3.38 (m, 1H, J_1=5.4 Hz, J_2=14.5 Hz, CH_2–Ph), 1.49 (s, 3H, Me), 1.45 (s, 3H, Me), 1.14 (s, 9H, 3Me), 0.98 (s, 9H, 3Me); ^{13}C NMR ($CDCl_3$) δ 174.0, 136.4, 130.5, 128.6, 127.2, 115.1, 83.8, 61.8, 56.6, 39.1, 37.0, 25.1, 23.2, 22.8, 21.1. Anal. Calcd for $C_{21}H_{33}NO_4S$: C, 63.76; H, 8.41; N, 3.54. Found: C, 63.94; H, 8.34; N, 3.58. The (5*R*)-configuration of (S_R)-**14** was assigned by homonuclear NOE experiments ($CDCl_3$). Upon irradiation of the acetal *tert*-butyl group at 0.98 ppm, relevant



(S_R, 2*S*, 5*R*, 1′*S*)-**14**

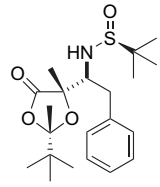
NOE effects (3 and 4.5%) were observed on the methyl protons at 1.49 and 1.45 ppm, respectively.

4.2.6. (S_S,2*S*,5*R*,1′*R*)-13 and (S_S,2*S*,5*S*,1′*S*)-15. The reaction of dioxolanone (2*S*,5*S*)-**1** (0.41 g, 2.41 mmol) with aldimine (S_S)-**6** (0.19 g, 0.86 mmol) yielded a 3.8/1.0 mixture of (S_S)-**13**/(S_S)-**15**. Silica gel chromatographic purification (*n*-hexane/EtOAc/CH_2Cl_2, 2/1/1) provided a 3.8/1.0 mixture of compounds (S_S)-**13**/(S_S)-**15** (0.25 g, 0.64 mmol, 75%) as an oil. (S_S,2*S*,5*R*,1′*R*)-**13**: IR ($CDCl_3$, cm^{-1}) 2957, 1771, 1290, 1154; MS *m*/*z* 395, 211, 193, 131, 91; ^1H NMR ($CDCl_3$) δ 7.25–7.10 (m, 5H, arom), 3.85–3.80 (m, 1H, H-1′), 3.72 (d, 1H, J_1=6.0 Hz, NH), 3.23 (dd, 1H, J_1=4.5 Hz, J_2=14.5 Hz, C*H*$_2$–Ph), 3.00 (dd, 1H, J_1= 8.0 Hz, J_2=14.5 Hz, C*H*$_2$–Ph), 1.48 (s, 3H, Me), 1.43 (s, 3H, Me), 1.10 (s, 9H, 3Me), 0.97 (s, 9H, 3Me); ^{13}C NMR ($CDCl_3$) δ 174.1, 137.3, 130.0, 128.7, 127.1, 114.8, 80.7, 62.1, 57.0, 39.2, 36.3, 24.9, 23.4, 22.8, 18.2. The (5*R*)-configuration of (S_S)-**13** was assigned by homonuclear NOE experiments ($CDCl_3$). Upon irradiation of the acetal *tert*-butyl group at 0.97 ppm, relevant NOE effects (4.5 and 2.5%) were observed on the methyl protons at 1.48 and 1.43 ppm, respectively.



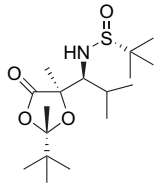
(S_S, 2*S*, 5*R*, 1′*R*)-**13**

(S_S,2*S*,5*S*,1′*S*)-**15**: IR ($CDCl_3$, cm^{-1}) 2960, 1775, 1290, 1152; MS *m*/*z* 395, 211, 193, 131, 91; ^1H NMR ($CDCl_3$) relevant resonances at δ 7.25–7.10 (m, 5H, arom), 4.49 (d, 1H, J_1=4.0 Hz, NH), 3.88–3.84 (m, 1H, H-1′), 3.04–2.92 (m, 2H, C*H*$_2$Ph), 1.62 (s, 3H, Me), 1.52 (s, 3H, Me), 1.10 (s, 9H, 3Me), 0.87 (s, 9H, 3Me); ^{13}C NMR ($CDCl_3$) δ 175.5, 138.5, 129.6, 128.6, 126.7, 116.0, 80.5, 60.6, 56.3, 38.9, 37.0, 25.0, 23.0, 22.9, 21.0. The (5*S*)-configuration of (S_S)-**15** was assigned by homonuclear NOE experiments ($CDCl_3$). Irradiation of the acetal *tert*-butyl group at 0.87 ppm produced a 1.5% NOE effect on the C2-methyl protons at 1.62 ppm. No NOE effect on the C5-methyl protons at 1.52 ppm was observed.



(S_S, 2*S*, 5*S*, 1′*S*)-**15**

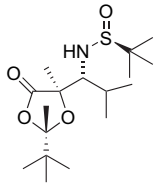
4.2.7. Synthesis of (S_R,2*S*,5*R*,1′*R*)-16, (S_R,2*S*,5*R*,1′*S*)-17, and (S_R,2*S*,5*S*,1′*S*)-18. The reaction of (2*S*,5*S*)-**1** (563 mg, 3.27 mmol) and imine (S_R)-**7** (206 mg, 0.756 mmol) afforded (S_R)-**16**/(S_R)-**17**/(S_R)-**18** as a 89/9/2 mixture. Chromatography (SiO_2, *n*-hexane/EtOAc, 4/3), gave the 1′-sulfinylimino dioxolanone (S_R)-**16** (206 mg, 0.593 mmol, 78%) and a 4.5/1 mixture of (S_R)-**17**/(S_R)-**18** (25 mg, 0.074 mmol, 10%) as a colorless oil. This mixture was used for the *N*-sulfinyl deprotection without any purification. (S_R,2*S*,5*R*,1′*R*)-**16**: white solid (mp 102–104 °C); $[\alpha]_D^{20}$ −102 (*c* 1.3, $CHCl_3$); IR (Nujol, cm^{-1}): 3240, 2965, 1788, 1470, 1400; HRMS *m*/*z* calcd for $C_{17}H_{33}NO_4S$ $[M]^+$: 347.2130, *m*/*z* found: 347.2125; ^1H NMR ($CDCl_3$) δ 4.35 (d, 1H, J_1=3.0 Hz, NH), 3.40 (t, 1H, J_1=J_2=3.0 Hz, H-1′), 2.16 (m, 1H, C*H*Me$_2$), 1.55 (s, 3H, Me), 1.43 (s, 3H, Me), 1.23 (s, 9H, 3Me, ^{t}BuSO), 1.08 (d, 3H, J=7.0 Hz, Me of CHMe$_2$), 1.00 (d, 3H, J=7.0 Hz, Me of CHMe$_2$), 0.96 (s, 9H, 3Me, ^{t}*Bu*CH); ^{13}C NMR ($CDCl_3$) δ 175.3, 115.8, 81.2, 62.4, 56.5, 38.9, 29.4, 25.0, 23.2, 23.1, 23.0, 20.2, 20.0. Anal. Calcd for $C_{17}H_{33}NO_4S$: C, 58.76; H, 9.57; N, 4.03. Found: C, 58.65; H, 9.55; N, 3.96. (S_R,2*S*,5*R*,1′*S*)-**17**: ^1H NMR ($CDCl_3$) δ 3.38–3.26 (m, 2H, NH and H-1′), 2.30 (m, 1H, C*H*Me$_2$), 1.61 (s, 3H, Me), 1.49 (s, 3H, Me), 1.23 (s, 9H, 3Me, ^{t}BuSO), 1.15 (d, 3H, J=7.0 Hz, Me of CHMe$_2$), 1.01–0.98 (m, 12H, 1Me of CHMe$_2$, and 3Me, ^{t}*Bu*CH); ^1H NMR (C_6D_6) δ 3.43 (dd, 1H, J_1=1.5 Hz, J_2=8.8 Hz, H-1′), 3.32 (d, 1H, J=8.8 Hz, NH), 2.11 (m, 1H, C*H*Me$_2$), 1.43 (s, 3H, Me), 1.27 (d, 3H, J=7.0 Hz, Me of CH*M*e$_2$), 1.26 (s, 3H, Me), 1.19 (s, 9H, 3Me, ^{t}BuSO), 0.97 (d, 3H, J=7.0 Hz, Me of CHMe$_2$), 0.85 (s, 9H, 3Me, ^{t}*Bu*CH); ^{13}C NMR ($CDCl_3$) δ 175.3, 115.2, 81.2, 67.0, 65.1, 39.2, 27.3, 25.3, 23.4, 23.3, 23.0, 22.2, 17.3. (S_R,2*S*,5*S*,1′*S*)-**18**: ^1H NMR (C_6D_6) relevant resonances at δ 3.62 (d, 1H, J=8.5 Hz, NH), 3.54 (dd, 1H, J_1=2.8 Hz, J_2=8.5 Hz, H-1′), 2.35 (m, 1H, C*H*Me$_2$), 1.38 (s, 3H, Me), 1.23 (s, 9H, 3Me, ^{t}BuSO), 0.95 (d, 3H, J=7.0 Hz, Me of CHMe$_2$), 0.86 (s, 9H, 3Me, ^{t}BuCH). The (5*R*)-configuration of (S_R)-**17** was assigned by homonuclear NOE experiments (C_6D_6). Irradiation of the acetal *tert*-butyl group at 0.85 ppm produced 3.0 and 2.0% NOE effects on the Me protons at 1.43 and 1.26 ppm, respectively.



(S_R, 2*S*, 5*R*, 1′*S*)-**17**

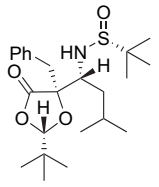
4.2.8. Synthesis of (S_S,2*S*,5*R*,1′*R*)-16. The reaction of (2*S*,5*S*)-**1** (300 mg, 1.74 mmol) and imine (S_S)-**7** (110 mg, 0.63 mmol) afforded (S_S)-**16**. Traces of a second diastereomer were observed by ^1H NMR spectroscopy of the crude material, but we could not isolate it from impurities. Chromatography (SiO_2, *n*-hexane/EtOAc, 4/3), gave the 1′-sulfinylimino dioxolanone (S_S)-**16** as a white solid (mp 138–140 °C) (214 mg, 0.618 mmol, 93%). $[\alpha]_D^{20}$ +63.1 (*c* 0.9, $CHCl_3$); IR (Nujol, cm^{-1}): 3244, 2963, 1790, 1470, 1395, 1282, 1251, 1153, 1049; HRMS *m*/*z* calcd for $C_{17}H_{33}NO_4S$ $[M]^+$: 347.2130, *m*/*z* found: 347.2121; ^1H NMR (C_6D_6) δ 3.40 (dd, 1H, J_1=3.2 Hz, J_2=8.8 Hz, H-1′), 3.29 (d, 1H, J=8.8 Hz, NH), 2.15 (m, 1H, C*H*Me$_2$), 1.24 (s, 3H, Me), 1.18 (d, 3H, J=7.0 Hz, Me of CHMe$_2$), 1.13 (s, 3H, Me), 1.12 (s, 9H, 3Me, ^{t}BuSO), 0.84 (d, 3H, J=7.0 Hz, Me of CHMe$_2$), 0.78 (s, 9H, 3Me, ^{t}*Bu*CH); ^{13}C NMR (C_6D_6) δ 172.6, 113.1, 81.3, 65.8, 56.4, 38.9, 27.9,

24.6, 22.8, 22.6, 22.5, 18.9, 18.5. Anal. Calcd for $C_{17}H_{33}NO_4S$: C, 58.76; H, 9.57; N, 4.03. Found: C, 58.81; H, 9.49; N, 4.09. The (5*R*)-configuration of (S_S)-**16** was assigned by homonuclear NOE experiments ($CDCl_3$). Irradiation of the acetal *tert*-butyl group at 0.96 ppm produced 3.5 and 4.8% NOE effects on the Me protons at 1.24 and 1.13 ppm, respectively.



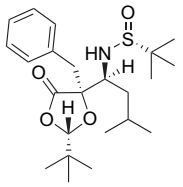
(S_S, 2*S*, 5*R*, 1′*R*)-**16**

4.2.9. Synthesis of (S_R,2*S*,5*R*,1′*R*)-19, (S_R,2*S*,5*R*,1′*S*)-20, and (S_R,2*S*,5*S*,1′*S*)-21. The dioxolanone (2*S*,5*S*)-**2** (335 mg, 1.43 mmol) was reacted with imine (S_R)-**5** (96 mg, 0.51 mmol). The ^{1}H NMR analysis of the crude mixture showed the presence of a 6.0/18.0/1.0 mixture of (S_R)-**19**/(S_R)-**20**/(S_R)-**21**. Silica gel purification (*n*-hexane/Et_2O, 1/1) afforded 119 mg of (S_R)-**20** (0.28 mmol, 55%) and 47 mg of a (S_R,)-**19**/(S_R)-**21**=6/1 mixture (0.11 mmol, 22%). (S_R,2*S*,5*R*,1′*R*)-**19**: pale oil; IR ($CDCl_3$, cm^{-1}) 1726; HRMS *m*/*z* calcd for $C_{23}H_{37}NO_4S$ $[M]^+$: 423.2443, *m*/*z* found: 423.2437; ^{1}H NMR ($CDCl_3$) δ 7.25–7.20 (m, 5H, arom), 5.33 (s, 1H, C2–H), 3.82 (d, 1H, *J*=7.0 Hz, NH), 3.58 (m, 1H, H-1′), 3.30 (d, 1H, *J*=14.5 Hz, CH_2–C_6H_5), 3.22 (d, 1H, *J*=14.5 Hz, CH_2–C_6H_5), 1.94–1.84 (m, 1H, Me_2CH), 1.66 (m, 1H, CH_2–$CHMe_2$), 1.50 (m, 1H, CH_2–$CHMe_2$), 1.27 (s, 9H, ^{t}BuS(O)), 0.95 (d, 3H, *J*=6.5 Hz, Me), 0.81 (d, 3H, *J*=6.5 Hz, Me), 0.62 (s, 9H, 3Me, ^{t}BuC2); ^{13}C NMR ($CDCl_3$) δ 173.9, 134.7, 131.2, 128.6, 127.3, 109.8, 85.5, 57.3, 57.0, 41.2, 39.0, 34.5, 25.3, 24.0, 23.3, 23.1, 21.2. The (5*R*)-configuration of (S_R,2*S*,5*R*,1′*R*)-**19** was assigned by homonuclear NOE experiments ($CDCl_3$). Irradiation of the hydrogen at C2-position (5.33 ppm) produced NOE effects (1.5 and 3.5%) on the NH (3.82 ppm) and H1′ (3.58 ppm), respectively.



(S_R, 2*S*, 5*R*,1′*R*)-**19**

(S_R,2*S*,5*R*,1′*S*)-**20**: pale oil; $[\alpha]_D^{20}$ −16.8 (*c* 0.7, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3220, 1721; HRMS *m*/*z* calcd for $C_{23}H_{37}NO_4S$ $[M]^+$: 423.2443, *m*/*z* found: 423.2430; ^{1}H NMR ($CDCl_3$) δ 7.25–7.15 (m, 5H, arom), 5.20 (s, 1H, C2–H), 3.68 (m, 1H, H-1′), 3.12 (d, 1H, *J*=12.0 Hz, CH_2–C_6H_5), 3.05 (d, 1H, *J*=12.0 Hz, CH_2–C_6H_5), 2.95 (d, 1H, *J*=5.0 Hz, NH), 1.96–1.85 (m, 1H, Me_2CH), 1.69 (m, 1H, CH_2–$CHMe_2$), 1.44 (m, 1H, CH_2–$CHMe_2$), 1.27 (s, 9H, ^{t}*Bu*S(O)), 0.99 (d, 3H, *J*=6.5 Hz, Me), 0.92 (d, 3H, *J*=6.5 Hz, Me), 0.58 (s, 9H, 3Me, ^{t}BuC2); ^{13}C NMR ($CDCl_3$) δ 173.2, 134.7, 131.2, 128.5, 127.3, 108.1, 86.5, 56.8, 56.3, 39.6, 36.9, 34.4, 24.2, 24.0, 23.3, 23.0, 21.1. Anal. Calcd for $C_{23}H_{37}NO_4S$: C, 65.21; H, 8.80; N, 3.31. Found: C, 65.17; H, 8.68; N, 3.20. The (5*R*)-stereoconfiguration of (S_R)-**20** was assigned by NOE experiments ($CDCl_3$). Irradiation of the *tert*-butyl group at C2-position (0.58 ppm) produced an NOE effect of 2.0% on the aromatic protons of the benzyl group, while irradiation of the hydrogen at C2-position (5.20 ppm) caused NOE effects (1.5 and 3.0%) on the NH (2.95 ppm) and H1′ (3.68 ppm), respectively.

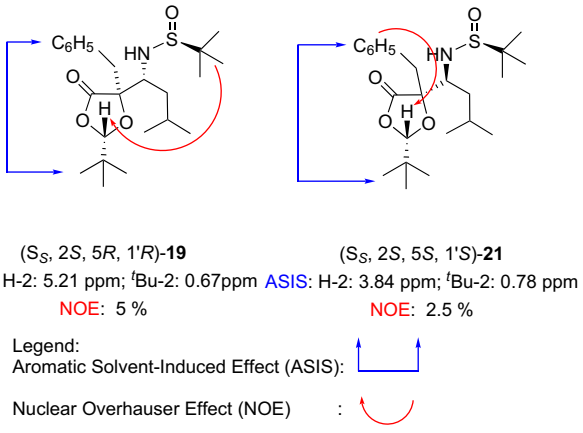


(S_R, 2*S*, 5*R*, 1′*S*)-**20**

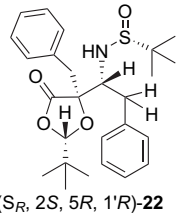
(S_R,2*S*,5*S*,1′*S*)-**21**: ^{1}H NMR ($CDCl_3$) relevant resonances at δ 5.22 (s, 1H, C2–H), 1.28 (s, 9H, ^{t}BuS(O)), 0.67 (s, 9H, 3Me, ^{t}BuC2).

4.2.10. Synthesis of (S_S,2*S*,5*R*,1′*R*)-19 and (S_S,2*S*,5*S*,1′*S*)-21. The dioxolanone (2*S*,5*S*)-**2** (525 mg, 2.24 mmol) was reacted with imine (S_S)-**5** (151 mg, 0.80 mmol). The ^{1}H NMR analysis of the crude compounds showed the presence of a 0.84/1.0 mixture of (S_S)-**19**/(S_S)-**21**. Silica gel purification (*n*-hexane/Et_2O, 1/1) afforded (S_S)-**19** (122 mg, 0.29 mmol, 36%) and (S_S)-**21** (145 mg, 0.34 mmol, 43%) as sticky oils. (S_S,2*S*,5*R*,1′*R*)-**19**: $[\alpha]_D^{20}$ +48.1 (*c* 0.5, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3215, 2966, 1726; HRMS *m*/*z* calcd for $C_{23}H_{37}NO_4S$ $[M]^+$: 423.2443, *m*/*z* found: 423.2433; ^{1}H NMR ($CDCl_3$) δ 7.30–7.18 (m, 5H, arom), 5.21 (s, 1H, C2–H), 3.59 (m, 1H, H-1′), 3.23 (d, 1H, *J*=14.0 Hz, CH_2–C_6H_5), 3.20 (d, 1H, *J*=6.0 Hz, NH), 3.09 (d, 1H, *J*=14.0 Hz, CH_2–C_6H_5), 1.94–1.84 (m, 1H, Me_2CH), 1.68–1.50 (m, 1H, CH_2–$CHMe_2$), 1.28 (s, 9H, ^{t}BuS(O)), 1.30–1.15 (m, 1H, CH_2–$CHMe_2$), 0.95 (d, 3H, *J*=6.5 Hz, Me), 0.80 (d, 3H, *J*=6.5 Hz, Me), 0.67 (s, 9H, 3Me, ^{t}BuC2); ^{13}C NMR ($CDCl_3$) δ 173.3, 134.5, 131.0, 128.6, 127.4, 109.5, 85.9, 57.7, 56.9, 41.0, 39.0, 34.6, 24.2, 23.9, 23.4, 23.1, 20.9. Anal. Calcd for $C_{23}H_{37}NO_4S$: C, 65.21; H, 8.80; N, 3.31. Found: C, 65.07; H, 8.76; N, 3.37. (S_S,2*S*,5*S*,1′*S*)-**21**: $[\alpha]_D^{20}$ +10.0 (*c* 0.6, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3210, 2963, 1772; HRMS *m*/*z* calcd for $C_{23}H_{37}NO_4S$ $[M]^+$: 423.2443, *m*/*z* found: 423.2436; ^{1}H NMR ($CDCl_3$) δ 7.30–7.25 (m, 5H, arom), 4.10 (d, 1H, *J*=6.4 Hz, NH), 3.84 (s, 1H, C2–H), 3.58 (m, 1H, H-1′), 3.57 (d, 1H, *J*=14.0 Hz, CH_2–C_6H_5), 3.12 (d, 1H, *J*=14.0 Hz, CH_2–C_6H_5), 1.95–1.84 (m, 1H, Me_2CH), 1.70–1.60 (m, 1H, CH_2–$CHMe_2$), 1.30 (s, 9H, ^{t}BuS(O)), 1.37–1.25 (m, 1H, CH_2–$CHMe_2$), 0.94 (d, 3H, *J*=6.4 Hz, Me), 0.92 (d, 3H, *J*=6.4 Hz, Me), 0.78 (s, 9H, 3Me, ^{t}BuC2); ^{13}C NMR ($CDCl_3$) δ 174.8, 134.8, 130.7, 128.8, 127.7, 109.9, 86.1, 59.3, 56.9, 41.5, 39.8, 34.5, 25.2, 24.0, 24.0, 23.2, 21.3. Anal. Calcd for $C_{23}H_{37}NO_4S$: C, 65.21; H, 8.80; N, 3.31. Found: C, 65.41; H, 8.88; N, 3.22. The (5*S*)-configuration of (S_S)-**21** was assigned by homonuclear NOE experiments ($CDCl_3$). Upon irradiation of the aromatic protons of the C5 benzyl group, significant NOE effect (2.5%) was observed at the H2 acetal proton. ASIS effect confirmed the structure: the shielding of the C2–H acetal

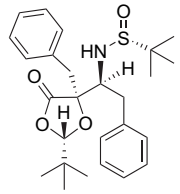
proton of (S_S)-**21** by the aromatic substituent (3.84 ppm) causes an upfield effect respect to that of (S_S)-**19** (5.21 ppm). Accordingly, the *C2-tert*-butyl substituent of (S_S)-**21** (0.78 ppm) was down-fielded respect to the one of (S_S)-**19** (0.67 ppm). The (5*R*)-stereoconfiguration of the epimer (S_S)-**19** was assessed by homonuclear NOE experiments. Upon irradiation of the *tert*-butyl group of the sulfinyl substituent at 1.28 ppm, a consistent NOE effect (5%) was observed at the H2 acetal proton at 5.21 ppm.



4.2.11. Synthesis of (S_R,2*S*,5*R*,1′*R*)-22, (S_R,2*S*,5*R*,1′*S*)-23, and (S_R,2*S*,5*S*,1′*S*)-24. The dioxolanone (2*S*,5*S*)-**2** (765 mg, 4.02 mmol) was reacted with imine (S_R)-**6** (259 mg, 1.17 mmol). The reaction was quenched after 60% conversion of the aldimine **6**. The ^{1}H NMR analysis of the crude reaction mixture showed the presence of a (S_R)-**22**/(S_R)-**23**/(S_R)-**24**=9.0/10.0/1.0 mixture. Silica gel purification (*n*-hexane/Et_2O, 1/1) afforded (S_R)-**22** (145 mg, 0.318 mmol, 27.0%) and a (S_R)-**23**/(S_R)-**24**=10/1 mixture (178 mg, 0.389 mmol). (S_R,2*S*,5*R*,1′*R*)-**22**: white solid (mp 98 °C); $[\alpha]_D^{20}$ +2.0 (*c* 0.8, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3218, 2960, 1731; HRMS *m/z* calcd for $C_{26}H_{35}NO_4S$ $[M]^+$: 457.2287, *m/z* found: 457.2274; ^{1}H NMR ($CDCl_3$) δ 7.40–7.15 (m, 8H, arom), 7.00 (m, 2H, arom), 5.61 (s, 1H, C2–H), 3.80 (m, 1H, H-1′), 3.57 (d, 1H, *J*=7.5 Hz, NH), 3.35 (s, 2H, 1′-CH_2–C_6H_5), 3.23 (dd, 1H, J_1=4.0 Hz, J_2=14.5 Hz, CH_2–C_6H_5), 2.88 (dd, 1H, J_1=10.4 Hz, J_2=14.5 Hz, CH_2–C_6H_5), 0.88 (s, 9H, ^{t}BuS(O)), 0.76 (s, 9H, 3Me, ^{t}BuC2); ^{13}C NMR ($CDCl_3$) δ 174.0, 138.0, 134.6, 131.0, 129.5, 128.9, 128.8, 127.6, 127.0, 110.5, 85.3, 61.6, 56.9, 40.0, 37.7, 34.8, 23.5, 22.4. Anal. Calcd for $C_{26}H_{35}NO_4S$: C, 68.24; H, 7.71; N, 3.06. Found: C, 68.36; H, 7.65; N, 3.14. The (5*R*)-stereoconfiguration of (S_S)-**22** was assigned by homonuclear NOE experiments ($CDCl_3$). Irradiation of the C2–H acetal proton (5.61 ppm) produced an NOE effect of 5.0% on the proton at the 1′-position (3.8 ppm), 3.0% on the NH proton (3.57 ppm), and 4.0% on the H proton of CH_2–C_6H_5 at 2.88 ppm.

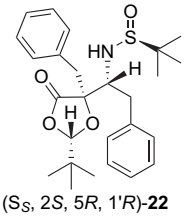

(S_R, 2*S*, 5*R*, 1′*R*)-**22**

(S_R,2*S*,5*R*,1′*S*)-**23**: sticky oil; IR ($CDCl_3$, cm^{-1}) 3218, 2960, 1725; HRMS *m/z* calcd for $C_{26}H_{35}NO_4S$ $[M]^+$: 457.2287, *m/z* found: 457.2295; ^{1}H NMR ($CDCl_3$) δ 7.40–7.18 (m, 10H, arom), 5.11 (s, 1H, C2–H), 4.00 (m, 1H, H-1′), 3.39 (dd, 1H, J_1=5.0 Hz, J_2=14.5 Hz, CH_2–C_6H_5), 3.30 (d, 1H, *J*=5.6 Hz, NH), 3.18 (m, 2H, CH_2–C_6H_5), 2.93 (dd, 1H, J_1=8.0 Hz, J_2=14.5 Hz, CH_2–C_6H_5), 1.16 (s, 9H, ^{t}BuS(O)), 0.55 (s, 9H, 3Me, ^{t}BuC2); ^{13}C NMR ($CDCl_3$) δ 173.3, 136.0, 134.6, 131.2, 130.2, 129.1, 129.0, 128.6, 127.4, 108.5, 86.8, 58.3, 56.6, 37.7, 36.8, 34.3, 23.2, 22.7. The (5*R*)-stereoconfiguration of (S_R)-**23** was assigned by homonuclear NOE experiments ($CDCl_3$). Irradiation of the C2–H acetal proton (5.11 ppm) produced an NOE effect of 7.0% on the proton at the 1′-position (4.0 ppm) and 3.0% on the NH proton (3.30 ppm).


(S_R, 2*S*, 5*R*, 1′*S*)-**23**

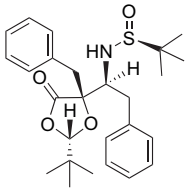
(S_R,2*S*,5*S*,1′*S*)-**24**: ^{1}H NMR ($CDCl_3$) relevant resonances at δ 5.21 (s, 1H, C2–H), 1.06 (s, 9H, ^{t}BuS(O)), 0.72 (s, 9H, 3Me, ^{t}BuC2); ^{13}C NMR ($CDCl_3$) relevant resonances at δ 136.4, 135.0, 130.9, 109.6, 85.4, 58.6, 57.1, 39.3, 37.0, 34.7, 23.5, 22.6.

4.2.12. Synthesis of (S_S,2*S*,5*R*,1′*R*)-22 and (S_S,2*S*,5*S*,1′*S*)-24. The dioxolanone (2*S*,5*S*)-**2** (942 mg, 4.02 mmol) was reacted with imine (S_S)-**6** (319 mg, 1.44 mmol). The ^{1}H NMR analysis of the crude material showed the presence of a 2.7/1.0 mixture of (S_S)-**22**/(S_S)-**24**. Silica gel purification (*n*-hexane/Et_2O, 1/1) afforded (S_S)-**22** (291 mg, 0.629 mmol, 43.7%) and (S_S)-**24** (107 mg, 0.233 mmol, 16.3%) as pale oils. (S_S,2*S*,5*R*,1′*R*)-**22**: $[\alpha]_D^{20}$ +72.5 (*c* 0.6, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3215, 2960, 1722; HRMS *m/z* calcd for $C_{26}H_{35}NO_4S$ $[M]^+$: 457.2287, *m/z* found: 457.2269; ^{1}H NMR ($CDCl_3$) δ 7.35–7.18 (m, 8H, arom), 7.14 (m, 2H, arom), 5.21 (s, 1H, C2–H), 3.93 (m, 1H, H-1′), 3.44 (d, 1H, *J*=4.8 Hz, NH), 3.32 (dd, 1H, J_1=4.8 Hz, J_2=14.4 Hz, 1′-CH_2–C_6H_5), 3.39 (d, 1H, *J*=14.4 Hz, CH_2–C_6H_5), 3.10 (d, 1H, *J*=14.4 Hz, CH_2–C_6H_5), 3.07 (dd, 1H, J_1=4.8 Hz, J_2=14.4 Hz, 1′-CH_2–C_6H_5), 1.07 (s, 9H, ^{t}BuS(O)), 0.72 (s, 9H, 3Me, ^{t}BuC2); ^{13}C NMR ($CDCl_3$) δ 173.2, 136.4, 134.5, 130.8, 129.9, 129.0, 128.8, 127.6, 127.4, 109.6, 85.4, 58.6, 56.6, 39.3, 37.0, 34.7, 23.5, 22.7. Anal. Calcd for $C_{26}H_{35}NO_4S$: C, 68.24; H, 7.71; N, 3.06. Found: C, 68.41; H, 7.78; N, 2.98. The (5*R*)-stereoconfiguration of (S_S)-**22** was assigned by homonuclear NOE experiments ($CDCl_3$). Irradiation of the C2–H acetal proton (5.21 ppm)


(S_S, 2*S*, 5*R*, 1′*R*)-**22**

produced an NOE effect of 4.0% on the proton at the 1′-position (3.93 ppm).

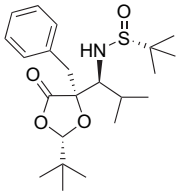
(S_S,2*S*,5*S*,1′*S*)-**24**: $[\alpha]_D^{20}$ −5.3 (*c* 0.4, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3215, 2960, 1725; HRMS *m*/*z* calcd for $C_{26}H_{35}NO_4S$ $[M]^+$: 457.2287, *m*/*z* found: 457.2294; ^1H NMR ($CDCl_3$) δ 7.35–7.10 (m, 10H, arom), 3.94–3.88 (m, 3H, 1H of C2–H and 2H of 1′-CH_2–C_6H_5), 3.71 (d, 1H, *J*=14.0 Hz, CH_2–C_6H_5), 3.18 (d, 1H, *J*=14.0 Hz, CH_2–C_6H_5), 3.03 (d, 1H, *J*=13.5 Hz, NH), 2.87 (m, 1H, H-1′), 1.02 (s, 9H, ^{t}BuS(O)), 0.80 (s, 9H, 3Me, ^{t}BuC2); ^{13}C NMR ($CDCl_3$) δ 176.0, 138.2, 134.7, 130.8, 129.9, 128.9, 128.7, 127.8, 126.9, 110.1, 86.3, 63.1, 56.8, 40.2, 38.7, 34.5, 23.9, 22.7. Anal. Calcd for $C_{26}H_{35}NO_4S$: C, 68.24; H, 7.71; N, 3.06. Found: C, 68.11; H, 7.80; N, 3.14. The (5*S*)-stereoconfiguration of (S_S)-**24** was assigned by NOE experiments ($CDCl_3$). Irradiation of the *tert*-butyl group at C2-position (0.80 ppm) produced an NOE effect of 1.8% on the proton at the 1′-position centered at 2.87 ppm and a cumulative NOE effect of 9.0% on the H-2 acetal proton and the 1′-CH_2–C_6H_5 protons (3.95–3.88 ppm).



(S_S, 2*S*, 5*S*, 1′*S*)-**24**

($CDCl_3$). Irradiation of the *tert*-butyl group at the C2-position (0.66 ppm) produced an NOE effect of 1.2% on the CH of the CH_2–C_6H_5 centered at 3.21 ppm and at the 1′-position centered at 2.87 ppm and an NOE effect of 1.5% on the aromatic protons.

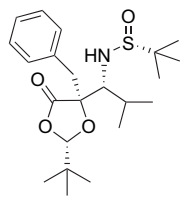
(S_R,2*S*,5*R*,1′*S*)-**26**: $[\alpha]_D^{20}$ −25.5 (*c* 0.6, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3210, 2955, 1726; HRMS *m*/*z* calcd for $C_{22}H_{35}NO_4S$ $[M]^+$: 409.2287, *m*/*z* found: 409.2272; ^1H NMR ($CDCl_3$) δ 7.30–7.18 (m, 5H, arom), 5.14 (s, 1H, C2–H), 3.45 (m, 2H, NH and H-1′), 3.15 (d, 1H, *J*=14.4 Hz, CH_2–C_6H_5), 3.10 (d, 1H, *J*=14.4 Hz, CH_2–C_6H_5), 2.37 (m, 1H, C*H*Me$_2$), 1.26 (s, 9H, ^{t}*Bu*S(O)), 1.14 (d, 3H, *J*=6.0 Hz, Me), 1.03 (d, 3H, *J*=6.0 Hz, Me), 0.61 (s, 9H, 3Me, ^{t}*Bu*C2); ^{13}C NMR ($CDCl_3$) δ 173.8, 134.6, 131.2, 128.6, 127.4, 109.4, 87.5, 65.3, 57.0, 39.9, 34.5, 27.4, 23.3, 23.0, .22.1, 17.1. The (5*R*)-stereoconfiguration of (S_R)-**26** was assigned by homonuclear NOE experiments ($CDCl_3$). Irradiation of the *tert*-butyl group at the C2-position (0.66 ppm) produced an NOE effect of 0.7% on the two protons of CH_2–C_6H_5 centered at 3.15 and 3.10 ppm, respectively, and an NOE effect of 1.7% on the aromatic protons.



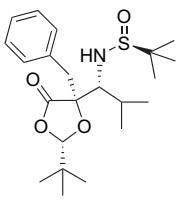
(S_R, 2*S*, 5*R*, 1′*S*)-**26**

4.2.13. Synthesis of (S_R,2*S*,5*R*,1′*R*)-25 and (S_R,2*S*,5*R*,1′*S*)-26. The dioxolanone (2*S*,5*S*)-**2** (565 mg, 2.41 mmol) was reacted with imine (S_R)-**7** (150 mg, 0.861 mmol). The ^1H NMR analysis of the crude material showed the presence of a 1.3/1.0 mixture of (S_R)-**25**/(S_R)-**26**. Silica gel purification (*n*-hexane/Et_2O, 1/1) afforded (S_R)-**25** as a sticky oil, contaminated by trace amounts of impurities (122 mg, 0.297 mmol, 34.5%), and (S_R)-**26** (93 mg, 0.228 mmol, 26.5%) as a pale sticky oil. (S_R,2*S*,5*R*,1′*R*)-**25**: IR ($CDCl_3$, cm^{-1}) 3200, 2950, 1734; HRMS *m*/*z* calcd for $C_{22}H_{35}NO_4S$ $[M]^+$: 409.2287, *m*/*z* found: 409.2266; ^1H NMR ($CDCl_3$) δ 7.23–7.18 (m, 5H, arom), 5.39 (s, 1H, C2–H), 3.75 (d, 1H, *J*=8.0 Hz, NH), 3.41 (dd, 1H, J_1=2.4 Hz, J_2=8.0 Hz, H-1′), 3.34 (d, 1H, *J*=14.8 Hz, CH_2–C_6H_5), 3.21 (d, 1H, *J*=14.8 Hz, CH_2–C_6H_5), 2.16 (m, 1H, C*H*Me$_2$), 1.28 (s, 9H, ^{t}BuS(O)), 1.00 (d, 3H, *J*=6.8 Hz, Me), 0.97 (d, 3H, *J*=6.8 Hz, Me), 0.66 (s, 9H, 3Me, ^{t}BuC2); ^{13}C NMR ($CDCl_3$) δ 173.8, 134.7, 131.3, 128.6, 127.4, 109.5, 86.1, 64.5, 57.5, 40.6, 34.6, 29.8, 23.4, .23.3, 23.0, 17.7. The (5*R*)-stereoconfiguration of (S_R)-**25** was assigned by homonuclear NOE experiments

4.2.14. Synthesis of (S_S,2*S*,5*R*,1′*R*)-25 and (S_S,2*S*,5*R*,1′*S*)-26. The dioxolanone (2*S*,5*S*)-**2** (984 mg, 4.20 mmol) was reacted with imine (S_S)-**7** (262 mg, 1.50 mmol). ^1H NMR analysis of the crude material showed the presence of a 7.75/1.0 mixture of (S_S)-**25**/(S_S)-**26**. Silica gel purification (*n*-hexane/Et_2O, 1/1) afforded (S_S)-**25** (380 mg, 0.930 mmol, 62.0%) and (S_S)-**26** (50 mg, 0.120 mmol, 8%) as a mixture with impurities. (S_S,2*S*,5*R*,1′*R*)-**25**: white sticky solid; $[\alpha]_D^{20}$ +32 (*c* 1.0, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3200, 2955, 1728; HRMS *m*/*z* calcd for $C_{22}H_{35}NO_4S$ $[M]^+$: 409.2287, *m*/*z* found: 409.2298; ^1H NMR ($CDCl_3$) δ 7.26–7.18 (m, 5H, arom), 5.16 (s, 1H, C2–H), 3.55 (d, 1H, *J*=8.8 Hz, NH), 3.44 (dd, 1H, J_1=2.0 Hz, J_2=8.8 Hz, H-1′), 3.19 (d, 1H, *J*=14.4 Hz, CH_2–C_6H_5), 3.14 (d, 1H, *J*=14.8 Hz, CH_2–C_6H_5), 2.20 (m, 1H, C*H*Me$_2$), 1.31 (s, 9H, ^{t}*Bu*S(O)), 1.12 (d, 3H, *J*=6.8 Hz, Me), 1.07 (d, 3H, *J*=6.8 Hz, Me), 0.59 (s, 9H, 3Me, ^{t}BuC2); ^{13}C NMR ($CDCl_3$) δ 173.0, 134.7, 131.2, 128.6, 127.4, 108.9, 87.0, 64.5, 57.2, 39.1, 34.4, 29.1, 23.3, .23.2, 22.4, 18.2. The (5*R*)-stereoconfiguration of (S_S)-**25** was assigned by homonuclear NOE experiments ($CDCl_3$). Irradiation of the *tert*-butyl group at the



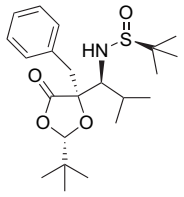
(S_R, 2*S*, 5*R*, 1′*R*)-**25**



(S_S, 2*S*, 5*R*, 1′*R*)-**25**

C2-position (0.59 ppm) produced an NOE effect of 1.6% on the aromatic protons.

(S_S,2*S*,5*R*,1′*S*)-**26**: IR ($CDCl_3$, cm^{-1}) 3210, 2950, 1731; HRMS *m*/*z* calcd for $C_{22}H_{35}NO_4S$ $[M]^+$: 409.2287, *m*/*z* found: 409.2297; ^1H NMR ($CDCl_3$) δ 7.45 (m, 2H, arom), 7.30–7.20 (m, 3H, arom), 5.21 (s, 1H, C2–H), 4.44 (d, 1H, *J*=8.5 Hz, NH), 3.53 (dd, 1H, J_1=2.0 Hz, J_2=8.5 Hz, H-1′), 3.38 (d, 1H, *J*=14.0 Hz, CH_2–C_6H_5), 3.27 (d, 1H, *J*=14.0 Hz, CH_2–C_6H_5), 2.15 (m, 1H, C*H*Me_2), 1.31 (s, 9H, ^{t}*Bu*S(O)), 0.94 (d, 3H, *J*=6.8 Hz, Me), 0.88 (d, 3H, *J*=6.8 Hz Me), 0.80 (s, 9H, 3Me, ^{t}BuC2); ^{13}C NMR ($CDCl_3$) δ 175.2, 134.7, 131.6, 128.5, 127.3, 110.0, 82.0, 64.3, 57.6, 39.8, 34.8, 28.6, 23.6, .23.3, 22.6, 16.2. The (5*R*)-stereoconfiguration of (S_S)-**25** was assigned by homonuclear NOE experiments ($CDCl_3$). Irradiation of the *tert*-butyl group at the C2-position (0.80 ppm) produced an NOE effect of 0.8% on one of the two protons of CH_2–C_6H_5 centered at 3.27 ppm and an NOE effect of 5.8% on the aromatic protons at 7.45 ppm.

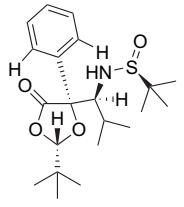


(S_S, 2*S*, 5*R*, 1′*S*)-**26**

4.2.15. Synthesis of (S_R,2*S*,5*R*,1′*S*)-27 and (S_S,2*S*,5*R*,1′*S*)-27. The dioxolanone (2*S*,5*S*)-**3** (143 mg, 0.65 mmol) was reacted with imine (S_{SR})-**5** (272 mg, 1.44 mmol). Silica gel column chromatography of the crude compound (*n*-hexane/EtOAc, 2/1) afforded a 1.5/1.0 mixture (229 mg, 0.56 mmol, 86%) of (S_R,2*S*,5*R*,1′*S*)-**27** and (S_S,2*S*,5*R*,1′*S*)-**27**. IR ($CDCl_3$, cm^{-1}) 3210, 1721; HRMS *m*/*z* calcd for $C_{22}H_{35}NO_4S$ $[M]^+$: 409.2287, *m*/*z* found: 409.2278. ^1H NMR ($CDCl_3$) δ 7.80–7.71 (m, 2H, arom, minor), 7.70–7.60 (m, 2H, arom, major), 7.41–7.23 (m, 3H, arom, major and minor), 5.52 (s, 1H, CH-2, minor), 5.45 (s, 1H, CH-2, major), 3.89–3.81 (m, 1H, H-1′, minor), 3.80–3.72 (m, 1H, H-1′, major), 3.35 (d, 1H, *J*=9.2 Hz, NH, minor), 3.08 (d, 1H, NH, major), 1.74–1.84 (m, 1H, Me_2C*H*, major), 1.72–1.62 (m, 1H, Me_2C*H*, minor), 1.42–1.26 (m, 4H, 2 CH_2, major and minor), 1.24 (s, 9H, 3Me, minor), 1.20 (s, 9H, 3Me, major), 0.95 (s, 9H, 3Me, minor), 0.94 (s, 9H, 3Me, major), 0.80 (d, 3H, *J*=6.4 Hz, Me, minor), 0.77 (d, 3H, *J*=6.8 Hz, Me, major), 0.67 (d, 3H, Me, minor), 0.63 (d, 3H, Me, major); ^{13}C NMR ($CDCl_3$) relevant resonances at δ 173.0 (major), 172.6 (minor), 136.3 (major), 135.7 (minor), 128.6 (major), 128.4 (minor), 126.2 (minor), 125.5 (major), 111.0 (major), 110.2 (minor), 86.7 (major), 85.0 (minor), 63.7 (major), 60.6 (minor), 57.2 (minor), 56.7 (major), 39.7 (major), 39.4 (minor), 35.7 (major), 35.5 (minor), 24.4 (minor), 23.9 (minor), 23.8 (major), 23.1 (major), 22.9 (major), 22.8 (minor), 21.0 (major), 20.8 (minor). Anal. Calcd for $C_{22}H_{35}NO_4S$: C, 64.51; H, 8.61; N, 3.42. Found: C, 64.55; H, 8.67; N, 3.48.

4.2.16. Synthesis of (S_R,2*S*,5*R*,1′*S*)-28 and (S_S,2*S*,5*R*,1′*S*)-28. The dioxolanone (2*S*,5*S*)-**3** (0.16 g, 0.71 mmol) was reacted with imine (S_{RS})-**6** (0.35 g, 1.56 mmol). Chromatography of the crude reaction mixture (SiO_2, *n*-hexane/EtOAc, 2/2) afforded a 13.0/1.0 mixture of (S_R,2*S*,5*R*,1′*S*)-**28** and (S_S,2*S*,5*R*,1′*S*)-**28** (0.24 g, 0.53 mmol, 75%). IR ($CDCl_3$, cm^{-1}) 3270–3201, 2961, 1793; MS *m*/*z* 443, 284, 193, 121, 105. ^1H NMR ($CDCl_3$) δ 7.88–7.84 (m, 2H, arom, minor), 7.82–7.68 (m, 2H, arom, major), 7.50–7.00 (m, 16H, arom, minor and major), 5.62 (s, 1H, H-2, minor), 5.30 (s, 1H, H-2, major), 4.30–4.16 (m, 1H, J_1=5.8 Hz, J_2=8.2 Hz, J_3=11.4 Hz, H-1′, major), 4.0–4.14 (m, 1H, H-1′, minor), 3.53 (d, 1H, NH, major), 3.25 (d, 1H, NH, minor), 2.96–2.82 (dd, 1H, CH_2–Ph, major), 2.80–2.66 (dd, 1H, CH_2–Ph, major), 2.41–2.28 (dd, 2H, CH_2–Ph, minor), 1.16 (s, 9H, 3Me, major), 0.99 (s, 9H, 3Me, minor), 0.93 (s, 9H, 3Me, major), 0.82 (s, 9H, 3Me, minor); ^{13}C NMR ($CDCl_3$) relevant resonances at δ 172.9 (major), 136.2 (major), 136.1 (major), 130.7 (major), 129.5 (minor), 128.7 (major), 128.4 (major), 126.9 (major), 126.1 (minor), 125.7 (major), 111.0 (major), 110.8 (minor), 86.7 (major), 65.2 (major), 57.0 (minor), 56.6 (major), 36.5 (major), 35.5 (major), 23.9 (minor), 23.8 (major), 22.7 (major), 22.1 (minor). Anal. Calcd for $C_{25}H_{33}NO_4S$: C, 67.69; H, 7.50; N, 3.16. Found: C, 67.65; H, 7.57; N, 3.21.

4.2.17. Synthesis of (S_S,2*S*,5*R*,1′*S*)-29. The reaction of dioxolanone (2*S*,5*S*)-**3** (394 mg, 1.79 mmol) and imine (S_S)-**7** (112 mg, 0.638 mmol) afforded compound (S_S,2*S*,5*R*,1′*S*)-**29** as a white solid (0.20 mg, 0.51 mmol, 80%). Mp 118–120 °C; $[\alpha]_D^{20}$ +2.8 (*c* 0.5, $CHCl_3$); IR (Nujol, cm^{-1}): 2960, 1793, 1202, 1081; HRMS *m*/*z* calcd for $C_{21}H_{33}NO_4S$ $[M]^+$: 395.5560, *m*/*z* found: 395.5566; ^1H NMR ($CDCl_3$) δ 7.70 (m, 2H, arom), 7.40–7.28 (m, 3H, arom), 5.52 (s, 1H, H-2), 3.77 (dd, 1H, J_1=1.6 Hz, J_2=10.4 Hz, H-1′), 3.55 (d, 1H, *J*=10.4 Hz, NH), 1.60–1.52 (m, 1H, C*H*Me_2), 1.26 (s, 9H, 3Me, ^{t}BuSO), 0.94 (s, 9H, 3Me, ^{t}*Bu*CH), 0.80 (d, 3H, Me, $CHMe_2$, *J*=7.0 Hz), 0.74 (d, 3H, Me, $CHMe_2$, *J*=7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 173.3, 137.4, 128.6, 128.4, 125.4, 111.2, 85.7, 67.3, 57.4, 35.5, 28.6, 24.0, 23.0, 22.0, 15.6. Anal. Calcd for $C_{21}H_{33}NO_4S$: C, 63.76; H, 8.41; N, 3.54. Found: C, 63.93; H, 8.35; N, 3.42. The (5*R*)-configuration of **29** was assigned by homonuclear NOE experiments ($CDCl_3$). Irradiation of the *C*2-*tert*-butyl group at 0.94 ppm produced a 2.5% NOE effect on the two *ortho* aromatic protons of the phenyl (7.70 ppm), while irradiation of H-2 at 5.52 ppm induced 2.0 and 2.5% NOE effects on the H-1′ and NH protons at 3.77 and 3.55 ppm, respectively.



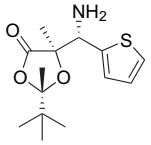
(S_S, 2*S*, 5*R*, 1′*S*)-**29**

4.3. General procedure for the synthesis of 1′-aminodioxolanones

Unless otherwise stated, to an MeOH solution of the *N*-sulfinylaminodioxolanone (2 mL×0.03 g of substrate) was

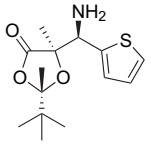
added an ethereal solution of 2 N HCl (16 equiv), under nitrogen and at 0 °C.[38] After 30 min, the temperature was raised to 25 °C and stirred for additional 2 h. The solvent was removed under vacuum and the residue was treated with a saturated aqueous solution of $NaHCO_3$, diluted with H_2O, and extracted three times with ethyl acetate. The organic phase was dried over Na_2SO_4 and the solvent removed under vacuum. Silica gel column chromatography of the residue yielded pure 1′-aminodioxolanones.

4.3.1. Synthesis of (2*S*,5*R*,1′*S*)-30. (i) *Deprotection of* (*S*$_S$,2*S*,5*R*,1′*S*)-**8**: a solution of (*S*$_S$)-**8** (60 mg, 0.15 mmol) was reacted with 1.25 mL of 2.0 N HCl (16.0 equiv). Chromatography of the crude reaction mixture (SiO_2, *n*-hexane/Et_2O, 1/1) provided (2*S*,5*R*,1′*S*)-**30** as an oil (36 mg, 0.13 mmol, 82%). (ii) *Deprotection of* (*S*$_R$,2*S*,5*R*,1′*S*)-**8**: the HCl-induced sulfinyl deprotection of (*S*$_R$)-**8** (75 mg, 0.19 mmol) afforded (2*S*,5*R*,1′*S*)-**30** (47 mg, 0.17 mmol, 82%). $[\alpha]_D^{20}$ +82.0 (*c* 0.26, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3390, 2959, 1782; MS *m*/*z* 283; ^1H NMR ($CDCl_3$) *δ* 7.27–7.22 (m, 1H, arom), 7.12–7.08 (m, 1H, arom), 7.04-7.0 (m, 1H, arom), 4.62 (s, 1H, H-1′), 1.92–1.85 (b, 2H, NH_2), 1.49 (s, 3H, Me), 1.45 (s, 3H, Me), 1.01 (s, 9H, 3Me); ^{13}C NMR ($CDCl_3$) *δ* 175.0, 143.4, 126.6, 125.5, 124.8, 115.2, 81.6, 57.2, 38.9, 24.8, 23.0, 17.8. Anal. Calcd for $C_{14}H_{21}NO_3S$: C, 59.34; H, 7.47; N, 4.94. Found: C, 59.60; H, 7.50; N, 4.86. The (5*R*)-stereoconfiguration of (2*S*,5*R*,1′*S*)-**30**, hence of the parent compounds (*S*$_R$)- and (*S*$_S$)-**8**, was assigned by homonuclear NOE experiments ($CDCl_3$). Upon irradiation of the *C*2-*tert*-butyl group at 1.01 ppm, significant NOE effects (5.5 and 3.5%) were observed on the Me protons at C2 (1.49 ppm) and C5 (1.47 ppm), respectively.



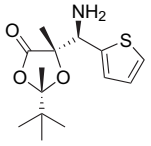
(2*S*,5*R*,1′*S*)-**30**

4.3.2. Synthesis of (2*S*,5*R*,1′*R*)-31. (i) *Deprotection of* (*S*$_R$,2*S*,5*R*,1′*R*)-**9**: a MeOH solution of (*S*$_R$)-**9** (45 mg, 0.12 mmol) was reacted with 0.09 mL of 2.0 N HCl (16.0 equiv). Silica gel column chromatography purification of the crude reaction mixture (*n*-hexane/Et_2O, 1/1) gave (2*S*, 5*R*, 1′*R*)-**31** as a sticky oil (28 mg, 0.10 mmol, 86%). (ii) *Deprotection of* (*S*$_S$,2*S*,5*R*,1′*R*)-**9**: after the HCl-induced deprotection of 10 mg of an MeOH solution of (*S*$_s$)-**9**, the ^1H NMR spectrum ($CDCl_3$) of the crude reaction mixture revealed the presence of (2*S*,5*R*,1′*R*)-**31**. $[\alpha]_D^{20}$ +49.0 (*c* 0.4, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3388, 1778; MS *m*/*z* 283; ^1H NMR ($CDCl_3$) *δ* 7.28–7.25 (m, 1H, arom), 7.05–7.00 (m, 1H, arom), 6.95–6.90 (m, 1H, arom), 4.43 (s, 1H, H-1′), 1.80–1.70 (b, 2H, NH_2), 1.79 (s, 3H, Me), 1.35 (s, 3H, Me), 1.03 (s, 9H, 3Me); ^{13}C NMR ($CDCl_3$) *δ* 175.0, 143.7, 126.2, 126.1, 125.4, 115.8, 83.7, 57.2, 39.0, 25.1, 22.3, 22.2. Anal. Calcd for $C_{14}H_{21}NO_3S$: C, 59.34; H, 7.47; N, 4.94. Found: C, 59.18; H, 7.41; N, 4.96. The (5*R*)-stereoconfiguration of **31** was assigned by homonuclear NOE experiments ($CDCl_3$). Irradiation of the *C*2-*tert*-butyl group at 1.03 ppm produced significant NOE effects (5.2 and 4.4%) on the CH_3 protons at C2 (1.79 ppm) and C5 (1.35 ppm), respectively.



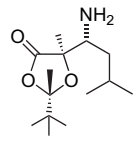
(2*S*, 5*R*, 1′*R*)-**31**

4.3.3. Synthesis of (2*S*,5*S*,1′*R*)-32. A MeOH solution of (*S*$_S$,2*S*,5*S*,1′*R*)-10 (80 mg, 0.2 mmol) was reacted with 1.6 mL of 2 N HCl (16 equiv). Silica gel column chromatography purification of the crude reaction mixture (*n*-hexane/Et_2O, 1/1) afforded (2*S*,5*S*,1′*R*)-**32** as a sticky foam (49 mg, 0.17 mmol, 83%). $[\alpha]_D^{20}$ −22.5 (*c* 0.68, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3390, 2959, 1780; MS *m*/*z* 283; ^1H NMR ($CDCl_3$) *δ* 7.28–7.23 (m, 1H, arom), 7.19–7.14 (m, 1H, arom), 7.04–7.00 (m, 1H, arom), 4.67 (s, 1H, H-1′), 1.99–1.50 (b, 2H, NH_2), 1.55 (s, 3H, Me), 1.49 (s, 3H, Me), 1.09 (s, 9H, 3Me); ^{13}C NMR ($CDCl_3$) *δ* 175.5, 142.7, 126.5, 125.4, 124.8, 115.2, 80.0, 56.1, 38.8, 24.8, 22.7, 18.0. Anal. Calcd for $C_{14}H_{21}NO_3S$: C, 59.34; H, 7.47; N, 4.94. Found: C, 59.11; H, 7.39; N, 5.01. The (5*S*)-stereoconfiguration of (2*S*,5*S*,1′*R*)-**32**, hence of (*S*$_S$,2*S*,5*S*,1′*R*)-**10** by chemical correlation, was assigned by homonuclear NOE experiments (CD_3COCD_3). This compound showed a significant NOE effect (5.0%) with the Me proton at C2 (1.55 ppm) upon irradiation of the *C*2-*tert*-butyl group at 1.09 ppm. Instead, no NOE effect was detected with the Me protons at C5 (1.49 ppm).



(2*S*, 5*S*, 1′*R*)-**32**

4.3.4. Synthesis of (2*S*,5*R*,1′*R*)-35. (i) *Deprotection of compound* (*S*$_S$,2*S*,5*R*,1′*R*)-**11**: a solution of (*S*$_S$)-**11** (90 mg, 0.25 mmol) was reacted with 2.0 mL of 2.0 N HCl (16 equiv). Silica gel chromatography of the crude reaction mixture (*n*-hexane/Et_2O, 1/1) afforded (2*S*,5*R*,1′*R*)-**35** (47 mg, 0.19 mmol, 73%). (ii) *Deprotection of compound* (*S*$_R$,2*S*,5*R*,1′*R*)-**11**: HCl-induced sulfinyl deprotection of (*S*$_R$)-**11** (80 mg, 0.22 mmol) provided (2*S*,5*R*,1′*R*)-**35** (47 mg, 0.18 mmol, 83%). Mp 98–101 °C; $[\alpha]_D^{20}$ +36.0 (*c* 0.36, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3349, 2965, 1775; mp 92 °C; MS *m*/*z* 257, 156, 130, 86. Anal. Calcd for $C_{14}H_{27}NO_3$: C, 65.33; H, 10.57; N, 5.44. Found: C, 65.51; H, 10.68; N, 5.46. ^1H NMR ($CDCl_3$) *δ* 3.06 (dd, 1H, J_1= 10.8 Hz, J_2=2.2 Hz, H-1′), 1.92–1.72 (m, 1H, Me_2CH), 1.52 (s, 3H, Me), 1.46–1.42 (b, 2H, NH_2), 1.39 (s, 3H, Me), 1.32–1.12 (m, 2H, CH_2), 0.99 (s, 9H, 3Me), 0.96 (d, 3H, *J*=6.8 Hz, Me), 0.89 (d, 3H, *J*=6.8 Hz, Me); ^{13}C NMR ($CDCl_3$) *δ* 175.5, 114.3, 81.4, 54.8, 39.6, 38.9, 24.7, 24.6, 24.0, 23.1, 21.1, 16.3. The (5*R*)-configuration of (*S*$_R$)-**15** was assigned by homonuclear NOE experiments. Irradiation of the acetal *tert*-butyl group at 0.99 ppm produced a 4.0 and 2.0% NOE effects on the Me protons at 1.52 and 1.39 ppm, respectively.



(S_S, 2*S*, 5*R*, 1′*R*)-**35**

4.3.5. Synthesis of (2*S*,5*R*,1′*S*)-36. (i) *Deprotection of compound* (S_S,2*S*,5*R*,1′*S*)-**12**: an MeOH solution of (S_S)-**12** (91 mg, 0.25 mmol) was reacted with 2.0 mL of 2.0 N HCl (16 equiv). Silica gel column chromatography of the crude reaction mixture (*n*-hexane/Et_2O, 1/1) provided (2*S*,5*R*,1′*S*)-**36** (56 mg, 0.22 mmol, 86%). (ii) HCl-induced sulfinyl deprotection of (S_S,2*S*,5*R*,1′*S*)-**12** (88 mg, 0.24 mmol) afforded (2*S*,5*R*,1′*S*)-**36** as a sticky oil (50 mg, 0.19 mmol, 80%). $[\alpha]_D^{20}$ +4.0 (*c* 0.35, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3349, 2965, 1775; MS *m*/*z* 257, 156, 130, 86; ^1H NMR ($CDCl_3$) δ 3.05 (dd, 1H, J_1=10.5 Hz, J_2=2.5 Hz, H-1′), 1.89–1.62 (m, 1H, Me_2CH), 1.62 (s, 3H, Me), 1.58–1.30 (m, 4H, $2CH_2$+NH_2), 1.36 (s, 3H, Me), 1.01 (s, 9H, 3Me), 0.96 (d, 3H, *J*=6.6 Hz, Me), 0.87 (d, 3H, Me); ^{13}C NMR ($CDCl_3$) δ 175.3, 114.8, 68.4, 55.0, 40.1, 39.2, 25.1, 24.9, 24.4, 23.1, 21.3, 18.7. Anal. Calcd for $C_{14}H_{27}NO_3$: C, 65.33; H, 10.57; N, 5.44. Found: C, 65.51; H, 10.61; N, 5.52.

4.3.6. Synthesis of (2*S*,5*R*,1′*R*)-37. A MeOH solution of (S_R)-**13** (0.10 g, 0.25 mmol) was reacted with 2.0 N HCl (16 equiv). Chromatography of the crude reaction mixture (SiO_2, *n*-hexane/EtOAc, 5/2+2% of isopropylamine) yielded (2*S*,5*R*,1′*R*)-**37** as a white solid (mp 79 °C) (0.066 g, 0.227 mmol, 91%). $[\alpha]_D^{20}$ +7.44 (*c* 0.39, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 2964, 1780, 1152; MS *m*/*z* 291, 232, 120, 92; ^1H NMR ($CDCl_3$) δ 7.30–7.20 (m, 5H, arom), 3.30 (m, 1H, H-1′), 3.14 (dd, 1H, J_1=2.0 Hz, J_2=13.2 Hz, CH_2–Ph), 2.42 (dd, 1H, J_1=10.8 Hz, J_2=13.2 Hz, CH_2–Ph), 1.62 (s, 3H, Me), 1.54 (s, 3H, Me), 1.56–1.50 (b, 2H, NH_2), 1.04 (s, 9H, 3Me); ^{13}C NMR ($CDCl_3$) δ 175.4, 139.3, 129.4, 128.9, 126.8, 115.0, 81.7, 59.1, 39.2, 37.4, 25.0, 23.5, 17.1. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.02; H, 8.60; N, 4.75.

4.3.7. Synthesis of (2*S*,5*R*,1′*S*)-38. An MeOH solution of (S_R,2*S*,5*R*,1′*S*)-**14** (0.16 g, 0.41 mmol) was reacted with 2.0 N HCl (16 equiv). Chromatography (SiO_2, *n*-hexane/EtOAc, 5/2+2% isopropylamine) yielded (2*S*,5*R*,1′*S*)-**38** as a sticky oil (0.10 g, 0.34 mmol, 85%). $[\alpha]_D^{20}$ −17.5 (*c* 0.40, CH_2Cl_2); IR ($CDCl_3$, cm^{-1}) 2964, 1783, 1152; MS *m*/*z* 291, 232, 120, 92; ^1H NMR ($CDCl_3$) δ 7.53–7.25 (m, 2H, arom), 7.23–7.18 (m, 3H, arom), 3.32–3.17 (m, 2H, 1 of H-1′ and 1H of CH_2–Ph), 2.36 (dd, 1H, J_1=5.4 Hz, J_2=6.6 Hz, CH_2–Ph), 1.66 (s, 3H, Me), 1.52 (s, 3H, Me), 1.42–1.31 (b, 2H, NH_2), 1.04 (s, 9H, 3Me); ^{13}C NMR ($CDCl_3$) δ 175.8, 139.0, 129.4, 128.9, 126.8, 115.3, 83.4, 58.5, 39.2, 37.6, 25.2, 22.9, 19.2. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.12; H, 8.71; N, 4.86.

4.3.8. Synthesis of (2*S*,5*S*,1′*S*)-39. An MeOH solution of a 3.8/1.0 mixture of (S_S,2*S*,5*R*,1′*R*)-**13**/(S_S,2*S*,5*S*,1′*S*)-**15** (0.11 g, 0.27 mmol) was reacted with 2.0 N HCl (16 equiv). Chromatography (SiO_2, *n*-hexane/EtOAc, 2/1) of the crude reaction mixture yielded a 3.8/1 mixture of (2*S*,5*R*,1′*R*)-**37**/(2*S*,5*S*,1′*S*)-**39** (0.069 g, 0.24 mmol, 88%). (2*S*,5*S*,1′*S*)-**39**: IR ($CDCl_3$, cm^{-1}) 1784, MS *m*/*z* 291; ^1H NMR ($CDCl_3$) δ 7.30–7.20 (m, 2H, arom), 7.23–7.18 (m, 3H, arom), 3.33 (m, 1H, H-1′), 3.10 (dd, 1H, J_1=2.0 Hz, J_2=13.0 Hz, CH_2–Ph), 2.40 (dd, 1H, J_1=10.5 Hz, J_2=13.2 Hz, CH_2–Ph), 1.61 (s, 3H, Me), 1.60 (s, 3H, Me), 1.56–1.50 (b, 2H, NH_2), 1.08 (s, 9H, 3Me); ^{13}C NMR ($CDCl_3$) δ 175.9, 139.1, 129.5, 128.9, 126.8, 115.0, 81.7, 57.8, 39.0, 37.2, 25.1, 23.1, 18.1.

4.3.9. Synthesis of (2*S*,5*R*,1′*R*)-40. (i) *Deprotection of compound* (S_S,2*S*,5*R*,1′*R*)-**16**: an MeOH solution of (S_S)-**16** (180 mg, 0.52 mmol) was reacted with 4.1 mL of 2.0 N HCl (16 equiv). The crude reaction mixture (107 mg, 0.44 mmol, 85%) of (2*S*,5*R*,1′*R*)-**40** was used for the next step without any further purification. (ii) *Deprotection of compound* (S_R,2*S*,5*R*,1′*R*)-**16**: an MeOH solution of (S_R)-**16** (120 mg, 0.35 mmol) was reacted with 2.7 mL of 2.0 N HCl (16 equiv) to afford 68 mg (0.28 mmol, 81%) of (2*S*,5*R*,1′*R*)-**40** as a white solid (mp 103–105 °C); HRMS *m*/*z* calcd for $C_{13}H_{25}NO_3$ $[M]^+$: 243.1834, *m*/*z* found: 243.1839; IR ($CDCl_3$, cm^{-1}) 2982, 1781; ^1H NMR ($CDCl_3$) δ 2.83 (d, 1H, *J*=4.8 Hz, H-1′), 2.03 (m, 1H, $CHMe_2$), 1.52 (s, 3H, Me), 1.44 (s, 3H, Me), 1.44–1.38 (b, 2H, NH_2), 1.04 (d, 3H, *J*=6.8 Hz, Me of $CHMe_2$), 1.00 (s, 9H, 3Me, ^{t}BuCH), 0.99 (d, 3H, *J*=6.8 Hz, Me of $CHMe_2$); ^{13}C NMR ($CDCl_3$) δ 176.0, 114.6, 82.3, 61.4, 39.0, 29.1, 25.0, 23.3, 22.7, 18.5, 17.5.

4.3.10. Synthesis of (2*S*,5*R*,1′*R*)-41. (i) *Deprotection of compound* (S_S,2*S*,5*R*,1′*R*)-**19**: HCl-induced sulfinyl deprotection of (S_S)-**19** (194 mg, 0.46 mmol) afforded (2*S*,5*R*,1′*R*)-**41** (133 mg, 0.42 mmol, 91%). (ii) *Deprotection of compound* (S_R,2*S*,5*R*,1′*R*)-**19**: HCl-induced sulfinyl deprotection of (S_R)-**19** (164 mg, 0.39 mmol) provided (2*S*,5*R*,1′*R*)-**41** (102 mg, 0.32 mmol, 82%). The crude oil **41** was used for the next step without any further purifications. (2*S*,5*R*,1′*R*)-**41**: IR ($CDCl_3$, cm^{-1}) 3355, 2965, 1772; HRMS *m*/*z* calcd for $C_{19}H_{29}NO_3$ $[M]^+$: 319.2147, *m*/*z* found: 319.2158; ^1H NMR ($CDCl_3$) δ 7.27–7.20 (m, 5H, arom), 5.34 (s, 1H, C2–H), 3.22 (d, 1H, *J*=14.5 Hz, CH_2–C_6H_5), 3.11 (dd, 1H, J_1=10.5 Hz, J_2=3.5 Hz, H-1′), 3.02 (d, 1H, *J*=14.0 Hz, CH_2–C_6H_5), 1.78–1.66 (m, 1H, Me_2CH), 1.54–1.25 (m, 4H, 2H of CH_2–$CHMe_2$ and 2H of NH_2), 0.98 (d, 3H, *J*=6.5 Hz, Me), 0.78 (d, 3H, *J*=6.5 Hz, Me), 0.73 (s, 9H, 3Me, ^{t}BuC2); ^{13}C NMR ($CDCl_3$) δ 174.6, 135.3, 131.0, 128.5, 127.2, 110.1, 86.6, 53.7, 40.8, 38.2, 34.7, 25.1, 24.4, 23.5, 21.1.

4.3.11. Synthesis of (2*S*,5*R*,1′*S*)-42. HCl-induced sulfinyl deprotection of (S_R,2*S*,5*R*,1′*S*)-**20** (126 mg, 0.30 mmol) afforded (2*S*,5*R*,1′*S*)-**42** (81 mg, 0.25 mmol, 85%). The crude oil **42** was used for the next step without any further purifications. (2*S*,5*R*,1′*S*)-**42**: $[\alpha]_D^{20}$ −30.0 (*c* 0.6, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3355, 2960, 1778; HRMS *m*/*z* calcd for $C_{19}H_{29}NO_3$ $[M]^+$: 319.2147, *m*/*z* found: 319.2140; ^1H NMR ($CDCl_3$) δ 7.27–7.20 (m, 5H, arom), 5.28 (s, 1H, C2-H), 3.17 (dd, 1H, J_1=10.5 Hz, J_2=2.5 Hz, H-1′), 3.08 (s, 2H, CH_2–C_6H_5), 1.85–1.66 (m, 1H, Me_2CH), 1.54–1.20 (m, 4H, 2H of CH_2–$CHMe_2$ and 2H of NH_2), 0.99 (d, 3H, *J*=6.5 Hz, Me), 0.87 (d, 3H, *J*=6.5 Hz, Me), 0.61 (s, 9H, 3Me, ^{t}BuC2); ^{13}C NMR ($CDCl_3$) δ 174.7, 135.3, 131.1,

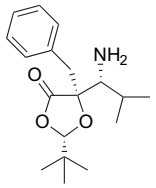
128.4, 127.1, 109.3, 87.2, 52.7, 40.2, 37.5, 34.4, 25.1, 24.3, 23.4, 21.2.

4.3.12. Synthesis of (2*S*,5*S*,1′*S*)-43. Sulfinyl deprotection of (*S*$_S$,2*S*,5*S*,1′*S*)-**21** (169 mg, 0.40 mmol) afforded (2*S*,5*S*,1′*S*)-**43** (104 mg, 0.33 mmol, 82%). The crude **43** was used for the next step without any further purifications. (2*S*,5*S*,1′*S*)-**43**: IR ($CDCl_3$, cm^{-1}) 3360, 1774; HRMS *m*/*z* calcd for $C_{19}H_{29}NO_3$ $[M]^+$: 319.2147, *m*/*z* found: 319.2133; ^1H NMR ($CDCl_3$) δ 7.30–7.25 (m, 5H, arom), 4.01 (s, 1H, C2–H), 3.24 (d, 1H, *J*=14.0 Hz, C*H*$_2$–C_6H_5), 3.08 (m, 1H, H-1′), 3.04 (d, 1H, *J*=14.0 Hz, C*H*$_2$–C_6H_5), 1.85–1.75 (m, 1H, Me_2CH), 1.82–1.75 (b, 2H, NH), 1.60–1.50 (m, 1H, C*H*$_2$–$CHMe_2$), 1.50–1.47 (m, 1H, C*H*$_2$–$CHMe_2$), 0.98 (d, 3H, *J*=6.2 Hz, Me), 0.88 (d, 3H, *J*=6.2 Hz, Me), 0.81 (s, 9H, 3Me, *t*-*Bu*C2); ^{13}C NMR ($CDCl_3$) δ 175.3, 135.2, 130.6, 128.8, 127.6, 109.3, 54.9, 40.4, 37.2, 34.6, 25.0, 24.4, 23.8, 21.2.

4.3.13. Synthesis of (2*S*,5*R*,1′*R*)-44. Sulfinyl deprotection of an MeOH solution of (*S*$_S$,2*S*,5*R*,1′*R*)-**22** (150 mg, 0.325 mmol) with 2.6 mL of 2.0 N HCl (16 equiv) afforded (2*S*,5*R*,1′*R*)-**44** as a sticky oil (0.100 mg, 0.286 mmol, 88%). The crude **44** was used for the next step without any further purifications. (2*S*,5*R*,1′*R*)-**44**: IR ($CDCl_3$, cm^{-1}) 3360, 1768; HRMS *m*/*z* calcd for $C_{22}H_{27}NO_3$ $[M]^+$: 353.1991, *m*/*z* found: 353.1983; ^1H NMR ($CDCl_3$) δ 7.40–7.20 (m, 8H, arom), 7.08 (m, 2H, arom), 5.43 (s, 1H, C2–H), 3.36–3.28 (m, 2H, 1H of 1′-C*H*$_2$–C_6H_5 and 1H of 5-C*H*$_2$–C_6H_5), 3.22–3.14 (m, 2H, 1H of 1′-C*H*$_2$–C_6H_5 and 1H of 5-C*H*$_2$–C_6H_5), 2.68 (m, 1H, H-1′), 0.82 (s, 9H, 3Me, *t*-*Bu*C2); ^{13}C NMR ($CDCl_3$) δ 174.4, 138.6, 135.3, 130.9, 129.3, 129.0, 128.7, 127.4, 126.9, 110.6, 86.2, 57.4, 39.0, 38.0, 34.9, 23.6.

4.3.14. Synthesis of (2*S*,5*S*,1′*S*)-45. Sulfinyl deprotection of an MeOH solution of (*S*$_S$,2*S*,5*S*,1′*S*)-**24** (95 mg, 0.207 mmol) with 1.7 mL of 2.0 N HCl (16 equiv) afforded (2*S*,5*S*,1′*S*)-**45** (0.60 mg, 0.172 mmol, 83%). The crude oil **45** was used for the next step without any further purifications. (2*S*,5*S*,1′*S*)-**45**: IR ($CDCl_3$, cm^{-1}) 3368, 1776; HRMS *m*/*z* calcd for $C_{22}H_{27}NO_3$ $[M]^+$: 353.1991, *m*/*z* found: 353.2004; ^1H NMR ($CDCl_3$) δ 7.35–7.20 (m, 10H, arom), 4.14 (s, 1H, C2–H), 3.37 (d, 1H, *J*=8.5 Hz, 5-C*H*$_2$–C_6H_5), 3.32 (d, 1H, *J*=8.0 Hz, 1′-C*H*$_2$–C_6H_5), 3.37 (d, 1H, *J*=8.5 Hz, 5-C*H*$_2$–C_6H_5), 3.14 (d, 1H, *J*=8.0 Hz, 1′-C*H*$_2$–C_6H_5), 2.72 (m, 1H, H-1′), 0.86 (s, 9H, 3Me, *t*-*Bu*C2); ^{13}C NMR ($CDCl_3$) δ 174.9, 138.9, 135.1, 130.7, 129.5, 128.9, 128.8, 127.6, 126.9, 109.5, 86.2, 58.4, 38.0, 37.4, 34.6, 23.8.

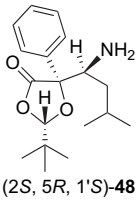
4.3.15. Synthesis of (2*S*,5*R*,1′*R*)-46. (i) *Deprotection of* (*S*$_s$,2*S*,5*R*,1′*R*)-**25**: sulfinyl deprotection of an MeOH solution of (*S*$_S$,2*S*,5*R*,1′*R*)-**25** (150 mg, 0.366 mmol) with 3.0 mL of 2.0 N HCl (16 equiv) afforded (2*S*,5*R*,1′*R*)-**46** (0.98 mg, 0.322 mmol, 88%). The crude oil **46** was used for the next step without any further purifications. (ii) *Deprotection of* (*S*$_R$,2*S*,5*R*,1′*R*)-**25**: after the HCl-induced deprotection of 15 mg of an MeOH solution of (*S*$_S$)-**25**, the ^1H NMR spectrum ($CDCl_3$) of the crude reaction mixture revealed the presence of (2*S*,5*R*,1′*R*)-**46** (2*S*,5*R*,1′*R*)-**46**: IR ($CDCl_3$, cm^{-1}) 3375, 1742; HRMS *m*/*z* calcd for $C_{18}H_{27}NO_3$ $[M]^+$: 305.1991, *m*/*z* found: 305.1987; ^1H NMR ($CDCl_3$) δ 7.26–7.18 (m, 5H, arom), 5.25 (s, 1H, C2–H), 3.29 (d, 1H, *J*=14.4 Hz, C*H*$_2$–C_6H_5), 3.06 (d, 1H, *J*=14.8 Hz, C*H*$_2$–C_6H_5), 2.93 (d, 1H, *J*=4.2 Hz, H-1′), 2.07 (m, 1H, C*H*Me_2), 1.05 (d, 3H, *J*=6.8 Hz, Me), 1.03 (d, 3H, *J*=6.8 Hz, Me), 0.62 (s, 9H, 3Me, *t*-*Bu*C2); ^{13}C NMR ($CDCl_3$) δ 174.7, 135.4, 131.2, 128.5, 127.1, 108.9, 87.0, 59.3, 37.6, 34.4, 29.8, 23.3, 22.4, 18.2. The (5*R*)-stereoconfiguration of (*S*$_S$)-**25** was assigned by NOE experiments ($CDCl_3$). Irradiation of the *tert*-butyl group at the C2-position (0.62 ppm) produced an NOE effect of 1.3% on the aromatic protons.



(2*S*, 5*R*, 1′*R*)-**46**

4.3.16. Synthesis of (2*S*,5*R*,1′*S*)-47. (i) *Deprotection of* (*S*$_R$,2*S*,5*R*,1′*S*)-**26**: sulfinyl deprotection of an MeOH solution of (*S*$_R$)-**26** (67 mg, 0.162 mmol) with 1.4 mL of 2.0 N HCl (16 equiv) afforded (2*S*,5*R*,1′*S*)-**47** (42 mg, 0.146 mmol, 90%). (ii) *Deprotection of* (*S*$_S$,2*S*,5*R*,1′*S*)-**26**; after the HCl-induced deprotection of 15 mg of an MeOH solution of (*S*$_S$)-**26**, the ^1H NMR spectrum ($CDCl_3$) of the crude reaction mixture revealed the presence of (2*S*,5*R*,1′*S*)-**47**. IR ($CDCl_3$, cm^{-1}) 3360, 1720; HRMS *m*/*z* calcd for $C_{18}H_{27}NO_3$ $[M]^+$: 305.1991, *m*/*z* found: 305.1979; ^1H NMR ($CDCl_3$) δ 7.25–7.18 (m, 5H, arom), 5.33 (s, 1H, C2–H), 3.11 (d, 1H, *J*=14.0 Hz, C*H*$_2$–C_6H_5), 3.07 (d, 1H, *J*=14.0 Hz, C*H*$_2$–C_6H_5), 2.96 (d, 1H, *J*=2.5 Hz, H-1′), 2.22 (m, 1H, C*H*Me_2), 0.99 (d, 3H, *J*=6.8 Hz, Me), 0.98 (d, 3H, *J*=6.8 Hz, Me), 0.62 (s, 9H, 3Me, *t*-*Bu*C2); ^{13}C NMR ($CDCl_3$) δ 175.9, 135.4, 131.2, 128.5, 127.2, 110.3, 87.9, 60.5, 40.0, 34.4, 28.0, 23.4, 22.2, 15.5.

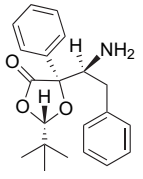
4.3.17. Synthesis of (2*S*,5*R*,1′*S*)-48. Deprotection of the 1.5/1.0 mixture of compounds (*S*$_R$,2*S*,5*R*,1′*S*)-**27** and (*S*$_R$,2*S*,5*R*,1′*S*)-**27** (166 mg, 0.41 mmol), followed by silica gel column chromatography purification (*n*-hexane/Et_2O, 1/1) afforded (2*S*,5*R*,1′*S*)-**48** as a white solid (mp 99–103 °C) (114 mg, 0.37 mmol, 92%). $[\alpha]_D^{20}$ −14.5 (*c* 1.05, $CHCl_3$); IR ($CDCl_3$, cm^{-1}); MS *m*/*z* 305, 220, 105, 77; ^1H NMR ($CDCl_3$) δ 7.80–7.60 (m, 2H, arom), 7.41–7.20 (m, 3H, arom), 5.59 (s, 1H, CH-2), 3.32 (dd, 1H, J_1=2.8 Hz, J_2=11.6 Hz, H-1′), 1.78–1.58 (m, 1H, Me_2CH), 1.42–1.28 (b, 2H, NH_2), 1.28–1.16 (m, 2H, CH_2), 0.96 (s, 9H, 3Me), 0.82 (d, 3H, *J*=6.8 Hz, Me), 0.66 (d, 3H, Me); ^{13}C NMR ($CDCl_3$) δ 174.5, 137.0, 128.3, 128.1, 125.5, 111.3, 87.4, 58.3, 39.8, 35.7, 24.4, 24.1, 23.9, 20.8. Anal. Calcd for



(2*S*, 5*R*, 1′*S*)-**48**

$C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.85; H, 8.83; N, 4.65. The (5*R*)-configuration of (2*S*,5*R*,1′*S*)-**48** was assigned by NOE experiments ($CDCl_3$). Irradiation of the *tert*-butyl group at the C2-position (0.96 ppm) produced NOE effect (4.5%) on the aromatic protons of the phenyl group (region between 7.27 and 7.20 ppm), while irradiation of the hydrogen at the C2-position (5.59 ppm) caused an NOE effect (3.0%) on the H1′ protons at 3.32 ppm.

4.3.18. Synthesis of (2*S*,5*R*,1′*S*)-49. Deprotection of the 13.0/1.0 mixture of compounds (*S*$_R$,2*S*,5*R*,1′*S*)-**28** and (*S*$_R$,2*S*,5*R*,1′*S*)-**28** (0.19 g, 0.43 mmol) followed by chromatography purification (SiO_2, *n*-hexane/EtOAc, 5/1) yielded (2*S*, 5*R*, 1′*S*)-**49** as a foaming sticky solid (0.11 g, 0.31 mmol, 72%). $[\alpha]_D^{20}$ +3.7 (*c* 0.33, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 2961, 1788, 1202; MS *m*/*z* 339, 324, 232, 120, 92. ^1H NMR ($CDCl_3$) δ 7.81–7.74 (m, 2H, arom), 7.47–7.35 (m, 3H, arom), 7.27–7.18 (m, 3H, arom), 7.07–7.02 (m, 2H, arom), 5.68 (s, 1H, H-2), 3.58 (dd, 1H, J_1=2.4 Hz, J_2=11.0 Hz, H-1′), 2.64–2.52 (dd, 1H, C*H*$_2$–Ph), 2.42–2.30 (dd, 1H, C*H*$_2$–Ph), 1.40–1.18 (b, 2H, NH_2), 1.00 (s, 9H, 3Me); ^{13}C NMR ($CDCl_3$) δ 174.1, 138.8, 137.0, 129.3, 128.8, 128.5, 128.3, 126.7, 125.5, 111.6, 86.7, 61.9, 37.4, 35.6, 23.9. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.27; H, 7.35; N, 4.09. The (5*R*)-configuration of (2*S*,5*R*,1′*S*)-**49** was assigned by homonuclear NOE experiments ($CDCl_3$). Irradiation of the hydrogen at the C2-position (5.68 ppm) caused an NOE effect (3.5%) on the H1′ protons at 3.58 ppm.



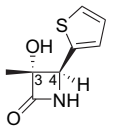
(2*S*, 5*R*, 1′*S*)-**49**

4.3.19. Synthesis of (2*S*,5*R*,1′*S*)-50. An MeOH solution of (*S*$_S$,2*S*,5*R*,1′*S*)-**29** (140 mg, 0.354 mmol) was reacted with 2.8 mL of 2.0 N HCl (16 equiv). The crude reaction mixture of the oil (2*S*,5*R*,1′*S*)-**50** (87 mg, 0.3 mmol, 84%) was used for the next step without any further purification. HRMS *m*/*z* calcd for $C_{17}H_{25}NO_3$ $[M]^+$: 291.1834, *m*/*z* found: 291.1846; IR (Nujol, cm^{-1}) 2958, 1784; ^1H NMR ($CDCl_3$) δ 7.70–7.60 (m, 2H, arom), 7.42–7.30 (m, 3H, arom), 5.57 (s, 1H, H-2), 3.27 (d, 1H, *J*=2.0 Hz, H-1′), 1.58–1.44 (m, 1H, C*H*Me$_2$), 1.36–1.26 (m, 2H, NH_2), 0.96 (s, 9H, 3Me, ^{t}*Bu*CH), 0.82 (d, 3H, Me, CHMe$_2$, *J*=6.8 Hz), 0.76 (d, 3H, Me, CHMe$_2$, *J*=6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 175.0, 137.5, 128.4, 128.0, 125.3, 111.3, 87.9, 64.2, 35.5, 27.6, 23.9, 21.8, 15.1.

4.4. General procedure for the synthesis of β-lactams

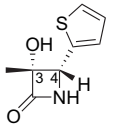
The β-lactams were prepared according to a modified literature procedure. The aminodioxolanone was dissolved in THF (1.0 mL×0.03 g of dioxolanone) at −30 °C. HMPA (0.1 mL×0.030 g of dioxolanone) was added dropwise, followed by LHMDS (4.0 equiv, 1 M THF solution). The temperature was raised to −5 °C during 3 h. The reaction was quenched with few drops of HCl (1.0 N) and warmed under stirring to room temperature. The reaction mixture was extracted with ethyl acetate (3×20 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, after filtration of the salts. The residue was purified by silica gel column chromatography to afford the β-lactam.

4.4.1. Synthesis of (3*R*,4*S*)-51. The reaction of compound (2*S*,5*R*,1′*S*)-**30** (50 mg, 0.18 mmol) was performed according to the reported standard procedure. Purification by silica gel column chromatography of the crude reaction mixture (EtOAc/*n*-pentane, 12/8) afforded the β-lactam (3*R*,4*S*)-**51** as a sticky oil (26 mg, 0.14 mmol, 81%). HRMS *m*/*z* calcd for $C_8H_9NO_2S$ $[M]^+$: 183.0354, *m*/*z* found: 183.0346; ^1H NMR ($CDCl_3$) δ 7.45–7.40 (m, 2H, arom), 7.02–7.10 (m, 2H, arom), 6.50–6.65 (br s, 1H, NH), 4.90 (s, 1H, H-4), 1.19 (s, 3H, Me); lit.[9b] relevant resonances at δ 4.91, 1.19; ^{13}C NMR (CD_3COCD_3) δ 173.2, 138.5, 127.5, 124.8, 124.7, 62.0, 54.3, 18.2. Homonuclear NOE experiments ($CDCl_3$) did not show any enhancement of the C4–*H* (4.90 ppm) upon irradiation of C3–Me at 1.19 ppm. Therefore, the stereochemistry of the β-lactam is (3*R*,4*S*). This allowed the stereochemical assessment of the parent dioxolanones (*S*$_R$,2*S*,5*R*,1′*S*)-**8** and (*S*$_S$,2*S*,5*R*,1′*S*)-**8**.



(3*R*,4*S*)-**51**

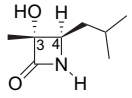
4.4.2. Synthesis of (3*R*,4*R*)-52. The reaction of compound (2*S*,5*R*,1′*R*)-**31** (45 mg, 0.159 mmol) was performed according to the reported standard procedure. Purification by silica gel column chromatography of the crude reaction mixture (SiO_2, EtOAc/*n*-pentane, 12/8) afforded β-lactam (3*R*,4*R*)-**52** as a white solid (24 mg, 0.13 mmol, 82%). Mp 190–192 °C; HRMS *m*/*z* calcd for $C_8H_9NO_2S$ $[M]^+$: 183.0354, *m*/*z* found: 183.0356; ^1H NMR ($CDCl_3$) δ 7.00–7.50 (m, 3H, arom), 6.40–6.55 (br s, 1H, NH), 4.84 (s, 1H, H-4), 2.70–2.78 (br s, 1H, OH), 1.64 (s, 3H, Me); lit.[9b] 7.00–7.50, 6.45–6.60, 4.83, 3.20–3.30, 1.63; ^{13}C NMR ($CDCl_3$) δ 172.0, 140.0, 127.9, 126.4, 126.2, 86.2, 61.6, 21.3; lit:[9b] 172.0, 139.9, 127.7, 126.1, 126.0, 86.0, 61.6, 21.2. Homonuclear NOE experiments ($CDCl_3$) performed on compound **52** showed, upon irradiation of CH_3 at C3 carbon atom (1.64 ppm), an enhancement of 4.8% of the hydrogen at the C4-position (4.84 ppm). Therefore, the stereochemistry of the β-lactam is (3*R*,4*R*). This allowed the stereochemical assessment of the parent dioxolanones (*S*$_R$,2*S*,5*R*,1′*R*)-**9** and (*S*$_S$,2*S*,5*R*,1′*R*)-**9**. Moreover, the stereochemical assessment of compounds (*S*$_S$,2*S*,5*R*,1′*S*)-**8** (from TS-I) and (*S*$_S$,2*S*,5*R*,1′*R*)-**9** (from TS-II), obtained by reaction of



(3*R*,4*R*)-**52**

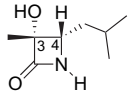
(2*S*)-**1a** with (S_S)-**4**, allowed the assessment of configuration of the third epimer (S_S,2*S*,5*S*,1′*R*)-**10** derived from TS-III.

4.4.3. Synthesis of (3*R*,4*R*)-53. LHMDS-induced cyclization of (2*S*,5*R*,1′*R*)-**35** (60 mg, 0.23 mmol) afforded, after silica gel column chromatography purification (EtOAc/*n*-hexane, 12/8), compound (3*R*,4*R*)-**53** as a pale yellow solid (30 mg, 0.19 mmol, 82%). Mp 136 °C; $[\alpha]_D^{20}$ +123.0 (*c* 0.44, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3339, 1748; MS *m*/*z* 157, 149, 86, 71; ^1H NMR (CD_3COCD_3) δ 7.25–7.15 (b, 1H, NH), 4.91 (s, 1H, OH), 3.54 (dd, 1H, J_1=8.0 Hz, J_2=4.0 Hz, H-4), 1.74–1.65 (m, 1H, Me_2CH), 1.49 (m, 1H, J_1=4.8 Hz, J_2=7.6 Hz, J_3=14.8 Hz, CH_2), 1.38 (m, 1H, CH_2), 1.27 (s, 3H, Me), 0.95 (d, 3H, *J*=6.0 Hz, Me), 0.93 (d, 3H, Me); ^{13}C NMR ($CDCl_3$) δ 172.6, 84.7, 61.7, 39.6, 26.4, 23.3, 22.5, 17.7. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.24; H, 9.55; N, 8.87. Homonuclear NOE experiments (CD_3COCD_3). Irradiation of OH at 4.91 ppm produced a 6.0% NOE effect on the CH-4 at 3.54 ppm. Therefore, the stereochemistry of the β-lactam is (3*R*,4*R*). This allowed the stereochemical assessment of the parent dioxolanones (S_R,2*S*,5*R*,1′*R*)-**11** and (S_R,2*S*,5*R*,1′*R*)-**11**.



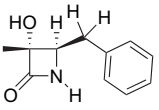
(3*R*, 4*R*)-**53**

4.4.4. Synthesis of (3*R*,4*S*)-54. Cyclization of (2*S*,5*R*,1′*S*)-**36** (82 mg, 0.32 mmol) afforded, after purification by silica gel column chromatography of the crude reaction mixture (EtOAc/cyclohexane, 3/1), the β-lactam (3*R*,4*S*)-**54** as a white solid (39 mg, 0.25 mmol, 78%). Mp 135 °C; $[\alpha]_D^{20}$ +19.5 (*c* 0.5, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3340, 1752; HRMS *m*/*z* calcd for $C_8H_{15}NO_2$ $[M]^+$: 157.1103, *m*/*z* found: 157.1107; ^1H NMR (CD_3COCD_3) δ 7.25–7.10 (b, 1H, NH), 4.80 (s, 1H, OH), 3.48 (dd, 1H, J_1=8.0 Hz, J_2=6.0, H-4), 1.76–1.64 (m, 1H, Me_2CH), 1.60–1.40 (m, 2H, CH_2), 1.42 (s, 3H, Me), 0.94 (d, 3H, *J*=6.0 Hz, Me), 0.92 (d, 3H, Me); ^{13}C NMR ($CDCl_3$) δ 173.3, 83.2, 61.3, 39.2, 25.9, 23.3, 22.7, 22.3. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.95; H, 9.53; N, 9.00. Homonuclear NOE experiments (CD_3COCD_3). Irradiation of Me at the C3-position (1.42 ppm) produced a 6% NOE effect on the hydrogen at C4-position (3.48 ppm). Accordingly, no NOE effect was detected on the hydrogen at C4-position upon irradiation of OH at 4.80 ppm, thus confirming the (3*R*,4*S*) β-lactam stereochemistry. This allowed the stereochemical assessment of the parent dioxolanones (S_R,2*S*,5*R*,1′*S*)-**12** and (S_R,2*S*,5*R*,1′*S*)-**12**.



(3*R*, 4*S*)-**54**

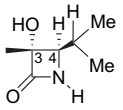
4.4.5. Synthesis of (3*R*,4*R*)-55. LHMDS-induced cyclization of (2*S*,5*R*,1′*R*)-**37** (0.082 g, 0.28 mmol) followed by chromatography purification of the residue (SiO_2, EtOAc/*n*-pentane, 3/13) afforded (3*R*,4*R*)-**55** as a white solid (0.045 mg, 0.23 mmol, 82%). Mp 172 °C; $[\alpha]_D^{20}$ +66.75 (*c* 0.65, CD_3COCD_3); IR ($CDCl_3$, cm^{-1}) 3321, 1757, 1234; MS *m*/*z* 191, 133, 105, 91; ^1H NMR (CD_3COCD_3) δ 7.34–7.12 (b, 1H, NH), 7.34–7.12 (m, 5H, arom), 5.04 (s, 1H, OH), 3.76 (dd, 1H, J_1=5.5 Hz, J_2=8.8 H-4), 3.02 (dd, 1H, J_1=5.5 Hz, J_2=14.4 Hz, CH_2–Ph), 2.77 (dd, 1H, J_1=8.8 Hz, J_2=14.4 Hz, CH_2–Ph), 1.38 (s, 3H, Me); ^{13}C NMR (CD_3COCD_3) δ 171.4, 138.9, 129.0, 128.7, 126.4, 84.5, 63.5, 37.2, 17.1. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.14; H, 6.81; N, 7.38. Homonuclear NOE experiments (CD_3COCD_3). Irradiation of C3–Me at 1.38 ppm produced an enhancement of 2.8 and 4.5% on CHs of CH_2–Ph centered at 3.02 and 2.77 ppm, respectively. Accordingly, irradiation of OH at 5.04 ppm induced a 2.3% NOE effect on the CH-4 at 3.76 ppm. Moreover, irradiation of one of the two CH protons of the benzylic group centered at 2.77 ppm produced a 1.5% enhancement on the C3–Me, while no NOE effect was observed on the OH group. Therefore, the stereochemistry of the β-lactam is (3*R*,4*R*). This allowed the stereochemical assessment of the parent dioxolanones (S_R,2*S*,5*R*,1′*R*)-**13** and (S_S,2*S*,5*R*,1′*R*)-**13**. Consequently, the stereochemistry of compounds (S_R,2*S*,5*R*,1′*S*)-**14** and (S_S,2*S*,5*S*,1′*S*)-**15** was also ascertained. In fact, both dioxolanones (S_R,2*S*,5*R*,1′*R*)-**13** and (S_R,2*S*,5*R*,1′*S*)-**14** were formed by reaction of (2*S*)-**1a** with aldimine (S_R)-**6**. These compounds only differed in their stereochemistry at the 1′-position since NOE experiments showed an identical (*R*)-stereoconfiguration at the 5-position. Instead, compounds (S_S,2*S*,5*R*,1′*R*)-**13** and (S_S,2*S*,5*S*,1′*S*)-**15** were formed by reaction of (2*S*)-**1a** with aldimine (S_S)-**6**. Since a (5*S*)-stereoconfiguration was assigned by NOE experiments to (S_S)-**15**, this compound is derived from TS-III. For this reason, a (*S*)-stereochemistry is found at the 1′-position.



(3*R*, 4*R*)-**55**

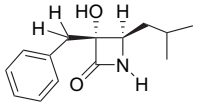
4.4.6. Synthesis of (3*R*,4*R*)-56. LHMDS-induced cyclization of (2*S*,5*R*,1′*R*)-**40** (102 mg, 0.42 mmol) followed by silica gel chromatography of the residue (*n*-hexane/EtOAc, 1/1) afforded the β-lactam (3*R*,4*R*)-**40** as a white solid (52 mg, 0.37 mmol, 87%). $[\alpha]_D^{20}$ +23.8 (*c* 0.5, CH_3COCH_3); mp 179–181 °C; IR (Nujol, cm^{-1}) 3400–3250, 1755; HRMS *m*/*z* calcd for $C_7H_{13}NO_2$ $[M]^+$: 143.0946, *m*/*z* found: 143.0958; ^1H NMR (CD_3COCD_3) δ 7.45–7.38 (b, 1H, NH), 4.99 (s, 1H, OH), 3.08 (d, 1H, *J*=10.4 Hz, H-4), 1.72–1.64 (m, 1H, C*H*Me_2), 1.35 (s, 1H, Me), 0.95 (d, 3H, *J*=6.0 Hz, 1Me of $CHMe_2$), 0.93 (d, 3H, *J*=6.0 Hz, 1Me of $CHMe_2$); ^{13}C NMR (CD_3COCD_3) δ 172.0, 83.9, 69.3, 29.8, 19.7, 18.9, 17.2. Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.64; H, 9.22; N, 9.90. Homonuclear NOE experiments (CD_3COCD_3). Irradiation of OH at 4.99 ppm produced a 6.5% NOE effect on the CH-4 at 3.08 ppm. Accordingly, the irradiation of C3–Me at 1.35 ppm induced a 2.5% enhancement of the CH of C*H*Me_2 centered at 1.68 ppm. Therefore, the stereochemistry of the β-lactam is (3*R*,4*R*). This allowed the

stereochemical assessment of the parent dioxolanone (S_R,2*S*,5*R*,1′*R*)-**16**. Consequently, the absolute configuration of (S_R,2*S*,5*R*,1′*S*)-**17** was also assessed since these epimers only differed in the stereochemistry at the 1′-position being both formed by reaction of (2*S*)-**1a** with aldimine (S_R)-**7** via TS-I and TS-II, respectively.



(3*R*, 4*R*)-**56**

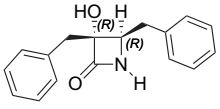
4.4.7. Synthesis of (3*R*,4*R*)-57. Cyclization of (2*S*,5*R*,1′*R*)-**41** (85 mg, 0.27 mmol) afforded, after purification by silica gel column chromatography of the crude reaction mixture (EtOAc/*n*-pentane, 12/8), the β-lactam (3*R*,4*R*)-**57** as a sticky oil (53 mg, 0.23 mmol, 85%). $[\alpha]_D^{20}$ +71 (*c* 0.5, CD_3COCD_3); IR ($CDCl_3$, cm^{-1}) 3336, 1747; HRMS *m*/*z* calcd for $C_{14}H_{19}NO_2$ $[M]^+$: 233.1416, *m*/*z* found: 233.1414; ^1H NMR (CD_3COCD_3) δ 7.46–7.30 (m, 3H, 2H arom and NH), 7.28–7.15 (m, 3H, arom), 4.91 (s, 1H, OH), 3.64 (dd, 1H, J_1=4.8 Hz, J_2=9.2 Hz, H-4), 3.11 (d, 1H, *J*=14.8 Hz, CH_2–C_6H_5), 2.99 (d, 1H, *J*=14.8 Hz, CH_2–C_6H_5), 1.72–1.60 (m, 1H, Me_2CH), 1.55–1.45 (m, 2H, CH_2–CH), 0.95 (d, 3H, *J*=6.5 Hz, Me), 0.92 (d, 3H, *J*=6.5 Hz, Me); ^{13}C NMR ($CDCl_3$) δ 171.0, 137.0, 130.8, 127.8, 126.2, 86.6, 61.5, 40.1, 37.8, 26.0, 23.1, 21.5. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.24; H, 8.15; N, 6.07. Homonuclear NOE experiments (CD_3COCD_3). Irradiation of OH at 4.91 ppm produced a 3.6% NOE effect on the hydrogen at C4-position (3.64 ppm). Accordingly, no NOE effect was observed on the C4–H hydrogen at 3.64 ppm upon irradiation of CH of CH_2–C_6H_5 (3.11 ppm and 2.99 ppm). Therefore, the stereochemistry of the β-lactam is (3*R*,4*R*). This allowed the stereochemical assessment of the parent 1′-aminodioxolanones (S_R,2*S*,5*R*,1′*R*)-**19** and (S_S,2*S*,5*R*,1′*R*)-**19**. Consequently, the stereochemistry of compound (S_R,2*S*,5*R*,1′*S*)-**20** was also assessed. In fact, NOE experiments showed a (5*R*)-stereochemistry for both (S_R,2*S*,5*R*,1′*R*)-**19** and (S_R,2*S*,5*R*,1′*S*)-**20**, derived from the same reaction. Hence, the two epimers differ in the stereochemistry at the 1′-position.



(3*R*, 4*R*)-**57**

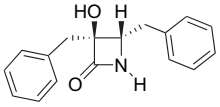
4.4.8. Synthesis of (3*S*,4*S*)-58. LHMDS-induced cyclization of (2*S*,5*S*,1′*S*)-**43** (105 mg, 0.34 mmol) afforded β-lactam (3*S*,4*S*)-**58** (62 mg, 0.27 mmol, 78%). Spectral data were identical to those reported for compound (3*S*,4*S*)-**58**. $[\alpha]_D^{20}$ −69 (*c* 0.5, CD_3COCD_3). This allowed the stereochemical assessment of the parent 1′-sulfinylamino-dioxolanone (S_R,2*S*,5*S*,1′*S*)-**21**.

4.4.9. Synthesis of (3*R*,4*R*)-59. Cyclization of (2*S*,5*R*,1′*R*)-**44** (110 mg, 0.311 mmol) afforded, after purification by silica gel column chromatography of the crude reaction mixture (EtOAc/*n*-pentane, 12/8), the β-lactam (3*R*,4*R*)-**59** as a white solid (73 mg, 0.274 mmol, 88%). $[\alpha]_D^{20}$ +73.5 (*c* 0.4, CD_3COCD_3); mp 139–140 °C; IR ($CDCl_3$, cm^{-1}) 3336, 1755; HRMS *m*/*z* calcd for $C_{17}H_{17}NO_2$ $[M]^+$: 267.1259, *m*/*z* found: 267.1245; ^1H NMR (CD_3COCD_3) δ 7.49 (m, 2H, arom), 7.35–7.25 (b, 1H, NH), 7.30–7.15 (m, 8H, arom), 5.03 (s, 1H, OH), 3.84 (dd, 1H, J_1=4.5 Hz, J_2=10.5 Hz, H-4), 3.26 (d, 1H, *J*=14.8 Hz, 3-CH_2–C_6H_5), 3.10 (d, 1H, *J*=14.8 Hz, 3-CH_2–C_6H_5), 3.06 (dd, 1H, J_1=4.5 Hz, J_2=14.0 Hz, 4-CH_2–C_6H_5), 2.84 (dd, 1H, J_1=10.5 Hz, J_2=14.0 Hz, 4-CH_2–C_6H_5); ^{13}C NMR ($CDCl_3$) δ 170.5, 138.9, 136.9, 130.9, 129.0, 128.8, 127.9, 126.5, 126.3, 86.5, 64.2, 37.7, 37.6. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.24; H, 6.35; N, 5.27. Homonuclear NOE experiments (CD_3COCD_3). Irradiation of OH at 5.03 ppm produced a 5.0% NOE effect on the hydrogen at C4-position (3.84 ppm). Therefore, the stereochemistry of the β-lactam is (3*R*,4*R*). This allowed the stereochemical assessment of the parent 1′-sulfinylamino-dioxolanone (S_R,2*S*,5*R*,1′*R*)-**22**.



(3*R*, 4*R*)-**59**

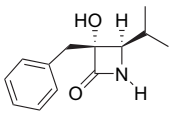
4.4.10. Synthesis of (3*S*,4*S*)-60. Cyclization of (2*S*,5*S*,1′*S*)-**45** (80 mg, 0.226 mmol) afforded, after purification by silica gel column chromatography of the crude reaction mixture (EtOAc/*n*-pentane, 12/8), the β-lactam (3*S*,4*S*)-**60** as a white solid (48 mg, 0.180 mmol, 81%). Mp 148–160 °C; $[\alpha]_D^{20}$ −74.1 (*c* 0.4, CD_3COCD_3); Spectral data were identical to those reported for compound (3*R*,4*R*)-**60**. This allowed the stereochemical assessment of the parent 1′-sulfinylamino-dioxolanone (S_S,2*S*,5*S*,1′*S*)-**24**.



(3*S*, 4*S*)-**60**

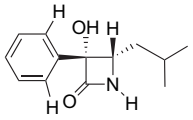
4.4.11. Synthesis of (3*R*,4*R*)-61. LHMDS-induced cyclization of (2*S*,5*R*,1′*R*)-**46** (110 mg, 0.360 mmol), followed by silica gel chromatography of the residue (*n*-hexane/EtOAc, 1:/1), the β-lactam (3*R*,4*R*)-**61** as a sticky oil (68 mg, 0.310 mmol, 87%). $[\alpha]_D^{20}$ +28 (*c* 0.5, CH_3COCH_3); IR (Nujol, cm^{-1}) 1747; HRMS *m*/*z* calcd for $C_{13}H_{17}NO_2$ $[M]^+$: 219.1259, *m*/*z* found: 219.1258; ^1H NMR (CD_3COCD_3) δ 7.44–7.40 (m, 3H, 2H arom and NH), 7.44–7.40 (m, 3H, arom), 4.93 (s, 1H, OH), 3.17 (d, 1H, *J*=10.4 Hz, H-4), 3.16 (d, 1H, *J*=14.4 Hz, CH_2–C_6H_5), 3.08 (d, 1H, *J*=14.4 Hz, CH_2–C_6H_5), 1.84–1.78 (m, 1H, CHMe$_2$), 0.94 (d, 6H, *J*=6.4 Hz, 2Me of CHMe$_2$); ^{13}C NMR (CD_3COCD_3) δ 171.0, 136.9, 130.9, 127.7, 126.3, 86.1, 69.8, 38.4, 19.8, 19.2. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.34; H, 7.92; N, 6.24. Homonuclear NOE experiments (CD_3COCD_3). Irradiation of OH at 4.93 ppm produced a 6.5% NOE effect on the CH-4 at 3.17 ppm. Therefore, the stereochemistry of the β-lactam is (3*R*,4*R*). This allowed the stereochemical assessment of

the parent 1′-sulfinylamino-dioxolanones (S_S,2*S*,5*R*,1′*R*)-**25** and (S_R,2*S*,5*R*,1′*R*)-**25**. Consequently, the stereochemistry of (S_R,2*S*,5*R*,1′*S*)-**26** and (S_S,2*S*,5*R*,1′*S*)-**26** were also assessed. In fact, both dioxolanones (S_R,2*S*,5*R*,1′*R*)-**25** and (S_R,2*S*,5*R*,1′*S*)-**26** were formed by reaction of (2*S*)-**1a** with aldimine (S_R)-**7**. These compounds only differed in their stereochemistry at the 1′-position since NOE experiments showed an identical (*R*)-stereoconfiguration at the 5-position. Similarly, dioxolanones (S_S,2*S*,5*R*,1′*R*)-**25** and (S_S,2*S*,5*R*,1′*S*)-**26** were formed by reaction of (2*S*)-**1a** with aldimine (S_S)-**7**. These compounds only differed in their stereochemistry at the 1′-position since NOE experiments showed an identical (*S*)-stereoconfiguration at the 5-position.



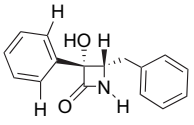
(3*R*, 4*R*)-**61**

4.4.12. Synthesis of β-lactam (3*R*,4*S*)-62. LHMDS-induced cyclization of (2*S*,5*R*,1′*S*)-**48** (114 mg, 0.37 mmol) afforded β-lactam (3*R*,4*S*)-**62** as a white solid (74 mg, 0.34 mmol, 90%). $[\alpha]_D^{20}$ −2.9 (*c* 0.4, CD_3COCD_3); IR ($CDCl_3$, cm^{-1}) 3350–3290, 1743; mp 218–220; *m*/*z* 219, 176, 133, 55; ^1H NMR (CD_3COCD_3) δ 7.76–7.58 (b, 1H, NH), δ 7.48 (m, 2H, arom), 7.39–7.20 (m, 3H, arom), 4.53 (s, 1H, OH), 3.73 (dd, 1H, J_1=11.6 Hz, J_2=15.2 Hz, H-4), 1.74–1.65 (m, 1H, CH_2), 2.05 (m, 2H, CH_2), 1.84–1.58 (m, 1H, Me_2CH), 0.95 (d, 3H, *J*=6.8 Hz, Me), 0.91 (d, 3H, Me); ^{13}C NMR ($CDCl_3$) δ 169.9, 141.2, 128.5, 127.8, 125.6, 61.8, 39.6, 25.4, 22.8, 22.2. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.24; H, 7.86; N, 6.44. Homonuclear NOE experiments (CD_3COCD_3). Irradiation of the two *ortho* protons of the phenyl group at 7.48 ppm produced a 4% NOE effect on the hydrogen at C4-position (3.73 ppm). Accordingly, no NOE effect was observed on C4–H upon irradiation of OH at 4.53 ppm. Therefore, the stereochemistry of the β-lactam is (3*R*,4*S*). This allowed the stereochemical assessment of the parent 1′-sulfinylamino-dioxolanones (S_R,2*S*,5*R*,1′*S*)-**27** and (S_S,2*S*,5*R*,1′*S*)-**27**.



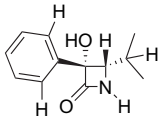
(3*R*,4*S*)-**62**

4.4.13. Synthesis of β-lactam (3*R*,4*S*)-63. LHMDS-induced cyclization of (2*S*,5*R*,1′*S*)-**49** (0.065 g, 0.19 mmol) followed by chromatography purification of the residue (SiO_2, *n*-hexane/EtOAc, 1/1) afforded β-lactam (3*R*,4*S*)-**63** as a pale yellow solid (0.034 mg, 0.14 mmol, 71%). $[\alpha]_D^{20}$ +14.6 (*c* 0.5, CD_3COCD_3); IR ($CDCl_3$, cm^{-1}) 3320–3280, 1745, 1452; mp 181 °C; *m*/*z* 253, 210, 192, 105, 77; ^1H NMR (CD_3COCD_3) δ 7.66 (s, 1H, NH), 7.52–7.46 (m, 2H, arom), δ 7.38–7.19 (m, 8H, arom), 5.79 (s, 1H, OH), 3.91 (dd, 1H, J_1=6.4 Hz, J_2=7.0 Hz, H-4), 3.25 (dd, 1H, J_2=14.4 Hz, CH_2–Ph), 2.95 (dd, 1H, CH_2–Ph); ^{13}C NMR ($CDCl_3$) δ 170.9, 140.8, 138.75, 129.5, 128.6, 128.5, 127.9, 126.4, 125.8, 64.6, 64.4, 37.1. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.91; H, 5.92; N, 5.58. Homonuclear NOE experiments (CD_3COCD_3). Irradiation of the OH group at 5.79 ppm produced 5 and 6% NOE effects on the two CH benzylic protons at 3.25 and 2.95 ppm, respectively. Irradiation of the H-4 proton at 3.91 ppm caused a 2.0% enhancement on the *ortho–ortho′* protons of the C3-phenyl group (7.49 ppm). Therefore, the stereochemistry of the β-lactam is (3*R*,4*S*). This allowed the stereochemical assessment of the parent 1′-sulfinylamino-dioxolanones (S_R,2*S*,5*R*,1′*S*)-**28** and (S_S,2*S*,5*R*,1′*S*)-**28**.



(3*R*, 4*S*)-**63**

4.4.14. Synthesis of (3*R*,4*S*)-64. LHMDS-induced cyclization of (2*S*,5*R*,1′*S*)-**50** (121 g, 0.41 mmol) followed by silica gel chromatography of the residue (SiO_2, *n*-hexane/EtOAc, 1/1), afforded β-lactam (3*R*,4*S*)-**64** as a white solid (75 mg, 0.36 mmol, 88%). $[\alpha]_D^{20}$ +57.2 (*c* 0.4, CH_3COCH_3); mp 206–208 °C; IR (Nujol, cm^{-1}) 3400–3250, 2956, 1746; HRMS *m*/*z* calcd for $C_{12}H_{15}NO_2$ $[M]^+$: 205.1103, *m*/*z* found: 205.1094; ^1H NMR (CD_3COCD_3) δ 7.84–7.75 (b, 1H, NH), 7.58–7.50 (m, 2H, arom), 7.32–7.25 (m, 1H, arom), 5.56 (s, 1H, OH), 3.23 (d, 1H, *J*=10.0 Hz, NH–C*H*), 2.10–2.00 (m, 1H, C*H*Me_2), 1.00 (d, 6H, *J*=6.4 Hz, 2Me of $CHMe_2$); ^{13}C NMR (CD_3COCD_3) δ 170.0, 141.4, 128.5, 127.7, 125.7, 87.2, 69.6, 29.5, 19.0, 18.6. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.04; H, 7.42; N, 6.90. Homonuclear NOE experiments (CD_3COCD_3). Irradiation of H-4 at 3.23 ppm produced a 2.5% NOE on the resonances of the two *ortho* aromatic protons at 7.54 ppm. Therefore, the stereochemistry of the β-lactam is (3*R*,4*S*). This allowed the stereochemical assessment of the parent 1′-sulfinylamino-dioxolanone (S_S,2*S*,5*R*,1′*S*)-**29**.



(3*R*, 4*S*)-**64**

4.5. General procedure for the synthesis of methyl β-sulfinylaminopropionates

To a solution of 1′-sulfinylamino-dioxolanone in dry methanol (3.0 mL×0.1 g) were added 1.5 equiv of an MeOH solution of MeO^- (1.5 M). The solution was stirred under nitrogen at 65 °C until disappearance of the starting material, which was monitored by TLC analysis. After cooling, the reaction mixture was quenched with 0.1 M HCl and extracted with ethyl acetate (3×15 mL). The combined organic phases were dried over Na_2SO_4 and after filtration the solvent was removed under vacuum. The residue was purified by silica gel flash column chromatography (SiO_2, EtOAc/*n*-hexane, 1/2) to afford the corresponding amino esters.

4.5.1. Synthesis of methyl 3-*tert*-butylsulfinyl-amino-2-hydroxy-2-methyl-4-phenylbutanoate ((*S*$_R$,2*R*,3*R*)-65). The MeO$^-$-induced methanolysis of (*S*$_R$,2*S*,5*R*,1′*R*)-**13** (100 mg, 0.25 mmol) provided (*S*$_R$,2*R*,3*R*)-**65** as a white solid (62 mg, 0.189 mmol, 75%). $[\alpha]_D^{20}$ +39.8 (*c* 0.5, $CHCl_3$); mp 198–200 °C; IR ($CDCl_3$, cm^{-1}) 3400, 1771, 1381, 1045; HRMS *m*/*z* calcd for $C_{16}H_{25}NO_4S$ $[M]^+$: 327.1504, *m*/*z* found: 327.1501; ^1H NMR ($CDCl_3$) δ 7.30–7.10 (m, 5H, arom), 4.80–4.20 (b, 1H, OH), 4.06 (d, 1H, *J*=9.5 Hz, NH), 3.78 (s, 3H, OMe), 3.63 (m, 1H, H-3), 2.87 (dd, 1H, J_1=3.5 Hz, J_2=14.0 Hz, CH_2Ph), 2.62 (dd, 1H, J_1=3.5 Hz, J_2=14.0 Hz, CH_2Ph), 1.61 (s, 3H, Me), 0.93 (s, 9H, 3Me, *t*-*Bu*S(O)); ^{13}C NMR ($CDCl_3$) δ 175.8, 138.3, 129.6, 128.6, 126.7, 76.4, 67.0, 56.4, 53.0, 39.0, 24.3, 22.6. Anal. Calcd for $C_{16}H_{25}NO_4S$: C, 58.69; H, 7.70; N, 4.28. Found: C, 58.64; H, 7.54; N, 4.22.

4.5.2. Synthesis of (*S*$_S$,2*R*,3*R*)-66. The MeO$^-$-induced methanolysis of (*S*$_S$,2*S*,5*R*,1′*R*)-**16** (90 mg, 0.26 mmol) provided (*S*$_S$,2*R*,3*R*)-**66** as a white solid (65 mg, 0.23 mmol, 90%). $[\alpha]_D^{20}$ +23.4 (*c* 0.3, $CHCl_3$); mp 127–129 °C; IR ($CDCl_3$, cm^{-1}) 3400, 1774, 1375, 1044; HRMS *m*/*z* calcd for $C_{12}H_{25}NO_4S$ $[M]^+$: 279.1504, *m*/*z* found: 279.1521; ^1H NMR ($CDCl_3$) δ 7.68–7.60 (m, 2H, arom), 7.42–7.25 (m, 3H, arom), 3.10 (s, 1H, NH), 3.78 (s, 3H, OMe), 3.64 (d, 1H, *J*=9.5 Hz, NH), 3.26 (d, 1H, *J*=9.5 Hz, H-4), 3.58–3.50 (b, 1H, OH), 1.76–1.68 (m, 1H, C*H*Me$_2$), 1.39 (s, 3H, Me), 1.27 (s, 9H, 3Me, *t*-*Bu*SO), 1.07 (d, 3H, *J*=6.8 Hz, Me of CHMe$_2$), 0.93 (d, 3H, *J*=6.8 Hz, Me of CHMe$_2$); ^{13}C NMR ($CDCl_3$) δ 176.8, 78.8, 67.5, 57.2, 53.2, 30.3, 25.2, 23.3, 22.1, 17.8. Anal. Calcd for $C_{12}H_{25}NO_4S$: C, 51.59; H, 9.02; N, 5.01. Found: C, 51.64; H, 9.10; N, 5.02.

4.5.3. Synthesis of (*S*$_S$,2*S*,3*S*)-67. The MeO$^-$-induced methanolysis of (*S*$_S$,2*S*,5*S*,1′*S*)-**21** (174 mg, 0.41 mmol) provided (*S*$_S$,2*S*,3*S*)-**67** as a sticky oil (0.13 g, 0.34 mmol, 83%). $[\alpha]_D^{20}$ +18.2 (*c* 0.6 $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3400, 2925, 1765, 1359, 1057; HRMS *m*/*z* calcd for $C_{19}H_{31}NO_4S$ $[M]^+$: 369.1974, *m*/*z* found: 369.1985; ^1H NMR ($CDCl_3$) δ 7.25–7.15 (m, 5H, arom), 3.99 (d, 1H, *J*=9.2 Hz, NH), 3.74 (s, 1H, OH), 3.72 (s, 3H, Me), 3.48 (m, 1H, H-3), 3.37 (d, 1H, *J*=14.0 Hz, C*H*$_2$–C$_6$H$_5$), 3.10 (d, 1H, *J*=14.0 Hz, C*H*$_2$–C$_6$H$_5$), 3.12 (d, 1H, *J*=14.0 Hz, C*H*$_2$–C$_6$H$_5$), 1.80–1.66 (m, 1H, Me$_2$C*H*), 1.51 (m, 1H, C*H*$_2$–CHMe$_2$), 1.27 (s, 9H, *t*-*Bu*S(O)), 0.95 (m, 1H, C*H*$_2$–CHMe$_2$), 0.89 (d, 3H, *J*=6.8 Hz, Me), 0.79 (d, 3H, *J*=6.4 Hz, Me); ^{13}C NMR ($CDCl_3$) δ 174.9, 136.0, 130.5, 128.3, 127.0, 80.6, 61.7, 57.0, 52.7, 41.5, 43.0, 42.1, 25.2, 24.4, 24.1, 23.2, 20.9. Anal. Calcd for $C_{19}H_{31}NO_4S$: C, 61.76; H, 8.46; N, 3.79. Found: C, 61.71; H, 8.39; N, 3.82.

4.5.4. Synthesis of (*S*$_S$,2*R*,3*S*)-68. The MeO$^-$-induced methanolysis of (*S*$_S$,2*S*,5*R*,1′*S*)-**29** (110 mg, 0.28 mmol) provided (*S*$_S$,2*R*,3*S*)-**68** as a white solid (82 mg, 0.24 mmol, 87%). $[\alpha]_D^{20}$ +87.8 (*c* 0.5, $CHCl_3$); mp 159–161 °C; IR ($CDCl_3$, cm^{-1}) 3400, 1781, 1355, 1060; HRMS *m*/*z* calcd for $C_{17}H_{27}NO_4S$ $[M]^+$: 341.1661, *m*/*z* found: 341.1647; ^1H NMR ($CDCl_3$) δ 7.68–7.60 (m, 2H, arom), 7.42–7.25 (m, 3H, arom), 4.22–4.18 (b, 1H, OH), 4.10 (s, 1H, NH), 3.87 (s, 3H, Me), 1.60–1.48 (m, 1H, C*H*Me$_2$), 1.27 (s, 9H, 3Me, *t*-*Bu*SO), 0.82 (d, 3H, Me, CHMe$_2$, *J*=7.2 Hz), 0.73 (d, 3H, Me, CHMe$_2$, *J*=13.5 Hz); ^{13}C NMR ($CDCl_3$) δ 174.7, 139.8, 128.6, 128.1, 125.6, 82.7, 65.9, 57.4, 54.5, 29.0, 23.4, 22.2, 15.9. Anal. Calcd for $C_{17}H_{27}NO_4S$: C, 59.80; H, 7.97; N, 4.10. Found: C, 59.64; H, 7.88; N, 4.02.

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