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Stereoselective One-Pot Synthesis of Constrained N,O-Orthogonally Protected *C*-Glycosyl Norstatines [C(1′)-Aminoglycosyl-1,3-dioxolan-4-ones]

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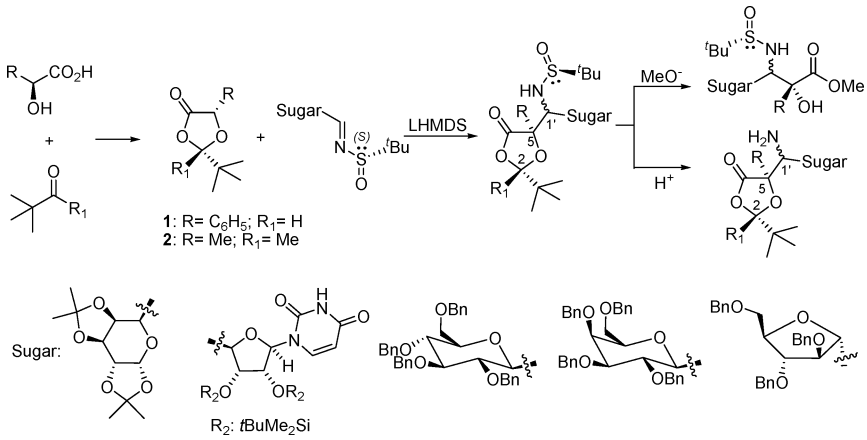

A procedure for the synthesis of conformationally constrained *C*-glycosyl norstatines has been developed. The key step of the reaction is the addition of (*S*)-*N*-sulfinyl azomethines to chiral (2*S*)-enolates of dioxolanones which exploits Seebach's "SRS" principle. The trisubstituted *C*-glycosyl-α-hydroxy-*β*-amino acids are formed as N,O-orthogonally protected 1′-glycosyl-sulfinylamino-dioxolan-4-ones, usually with high diastereomeric excesses. Both the sulfinyl group at the nitrogen atom and the acetal moiety of the dioxolanone ring were selectively removed, thus demonstrating the orthogonality of the two protecting groups. In fact, the MeO^- induced methanolysis of the acetal group gave the corresponding methyl *C*-glycosyl-sulfinylamino-isoserinates, while the acid induced removal of the sulfinyl group gave the N-deprotected 1′-glycosylamino-dioxolan-4-ones, which were in several cases subjected to a one-pot base-induced cyclization yielding the corresponding glycosyl-*β*-lactams. This allowed the stereochemical configuration assessment of the parent 1′-glycosyl-sulfinylamino-dioxolan-4-ones by chemical correlation methods or by NOE experiments performed on the *β*-lactams.

Introduction

Glycosamino acids (GAAs) are molecules which combine the structural features of simple amino acids with those of simple carbohydrates.[1] The resulting hybrid is a highly functionalized building block, which can be used for the synthesis of glycopeptides by means of combinatorial chemistry.[2]

Several efforts have been dedicated to the synthesis of nonnatural *C*-glycosyl amino acids in which the amino acid side chain is connected to the sugar moiety via a carbon−carbon bond, to construct C-linked glycoconjugates, more stable toward glycosidases with respect to the natural O- or N-linked glycoamino acids. The corresponding *C*-glycopeptides display an increased stability toward chemical and enzymatic cleavage with respect to the natural O- and N-linked counterparts,[3] as well as solution conformations[4] and biological activities similar to the naturally occurring glycopeptides. Selected examples are peptidyl nucleosides which display antibiotic activity;[5] galactosphingolipid analogues, which specifically bind to HIV-1 gpl20;[6]

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neuraminidase-resistant *C*-glycosides of sialic acid, which strongly inhibit the in vitro infectivity of influenza virus;[7] C-mannose mimicking analogues of sialyl Lewis X;[8] and high-mannose-type C-linked glycopeptide analogues, which show inhibitory activity toward glycoamidases of plants, bacterials, and animals.[9] In this context, glycosyl β-amino acids represent rewarding synthetic targets, because they introduce a further diversification into the *C*-glycopeptides frame. These oligomers have a potential as peptidomimetics, since, unlike α-amino acid peptides, they are stable to peptidases and are more conformationally rigid.[10] Moreover, their structures can be tuned by changing the side chain position in the monomer skeleton. Only a few strategies for the synthesis of glycosyl β-amino acids are available so far, which are based on a Michael-type addition of amines to sugar derived α,β-unsaturated esters:[11] reaction of α-amido glycoalkyl sulfones with the lithium enolate derived from 2-acetylisoborneol,[12] and Mannich-type and Reformatsky-type reactions.[13]

Our interest in this field is focused on the synthesis of conformationally constrained trisubstituted α-hydroxy-$\beta^{2,2,3}$-amino acids hybrids connected to a *C*-glycosyl scaffold in order to combine sugar properties, such as good pharmacokinetics[14] and transport capabilities,[15] with the structural features of the α-hydroxy-β-amino acids (norstatines). It is worth noting that norstatines exhibit a "per se" inhibitory activity against aminopeptidase-2 (MetAP2) which is involved in angiogenesis,[16] also they can be used as building blocks to generate oligopeptides employed in the design of protease inhibitors including renin,[17] HIV retropepsins,[18] plasmepsins,[19] and cathepsins.[20] These proteases are involved in several important pathologies regarding blood pressure regulation, HIV, malaria, and Alzehimer's disease. Furthermore, the restriction of the conformational flexibility, which is provided by the presence of an additional substituent at the C2-carbon atom, plays an important role in drug design for the binding of peptidomimetics to protein receptors. Compounds that are too flexible may generate a binding complex with high entropic energy, which can render the process energetically unfavorable. The literature reports examples about the importance of conformational restriction on the biological activity of disubstituted $\beta^{2,2}$- and trisubstituted $\beta^{2,2,3}$-amino acids in the field of HIV-1 protease inhibitors toward sensitive and resistant cell lines,[21] as fibrinogen receptor antagonists[22] and as inhibitors of platelet aggregation,[23] and, more specifically, on the biological activity of trisubstituted α-hydroxy-$\beta^{2,2,3}$-amino acids.[24]

We report herein the synthesis of glycosamino acids obtained by incorporation of side chains of conformationally constrained chiral α-hydroxy-$\beta^{2,2,3}$-amino acids into hydroxyl protected carbohydrate-based five- or six-membered scaffolds and, in particular, into an uridine nucleobase. The introduction of hydrophobic components into the hydroxyl groups of the carbohydrate could increase the lipophilicity of the molecules, rendering them more likely to permeate cell membranes. At the same time, the chelating groups OH, COOH, and NH_2 of the isoserine moiety might be involved in coordination to metal ions, often found in the enzyme's active site.

To date, the methodologies for the synthesis of *C*-glycosyl norstatines are lacking. The few available protocols concern the synthesis of disubstituted *C*-glyco α-hydroxy-β^{-}amino acids and are based on the β-lactam synthon method (β-LSM),[25] namely, via ring opening of 3-alkoxy-β-lactams, which are obtained by sugar aldimines cycloaddition to a limited number of alkoxyketenes, according to Staudinger's protocol.[26] However, the cycloaddition rarely allows full diastereocontrol of the reaction outcome[26a,b] and usually cis-isomers are obtained as major products.[26c,d] Therefore, the development of more general and selective methodologies is of absolute importance, especially for the synthesis of anti-isomers.

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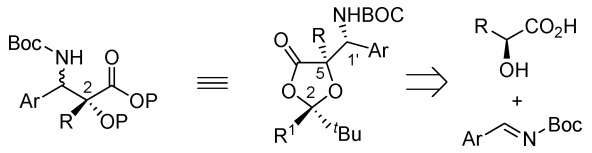
SCHEME 1



Results and Discussion

An alternative protocol to the β-lactam synthon method is based on the addition of imines to ester enolates. Surprisingly, this protocol has not been thoroughly investigated,[27] even if this route provides disubstituted norstatines in a one-pot reaction, simply through a proper choice of the electrophilic substituents at the imine nitrogen atom. A modification of this protocol makes use of aromatic and heteroaromatic Boc-aldimines as the partners of chiral ester enolates of natural (*S*)-α-hydroxy acids, namely the (2*S*)-enolates of 1,3-dioxolan-4-ones,[28] affording N-substituted *C*-(1′)-amino-1,3-dioxolan-4-ones, which can be considered as N,O-orthogonally protected trisubstituted α-hydroxy-β[2,2,3]-amino acids analogues (Scheme 1). This protocol could have been applied to the synthesis of conformationally constrained *C*-glycosyl isoserines, but unfortunately Boc-aldimines proved to be inadequate for this aim, since their synthesis involves the use of strong acidic conditions, which are unsuitable with some of the substrates employed in the present work.[12]

To prevent this inconvenience, the sulfinyl N-protecting group attracted our attention, since it is widely employed for the synthesis of stable and electrophilically activated aliphatic imines.[29] In particular, the *tert*-butanesulfinamide was selected as the precursor of *C*-glycosyl aldimines.[30] Preliminary experiments carried out with enolate **1a** (Scheme 2) and imines derived from the condensation of the heteroaromatic 2-thiophene aldehyde with (S_S)-, and (S_R)-*N*-*tert*-butanesulfinyl amides, showed that better diastereoselection was achieved with the (S_S)-*N*-*tert*-butanesulfinyl aldimine. For this reason, this amide was selected for the synthesis of sugar imines **8**−**12** from the corresponding aldehydes: β-D-*C*-gluco-pyranoside (**3**),[31] β-D-*C*-galacto-pyranoside (**4**),[31] α-D-*C*-arabinofuranoside (**5**),[32,33] nonanomeric 1,2,3,4-di-*O*-isoproylidene-α-D-galactohexo-dialdo-1,5-pyranose (**6**),[26a] and the 3,4-di-*O*-(*tert*-butyl-dimethylsilyl)-uridine-5-carboxaldehyde (**7**) (Figure 1).

For the present study two dioxolanones with different steric demand were employed as sugar imines (**8**−**12**) reaction

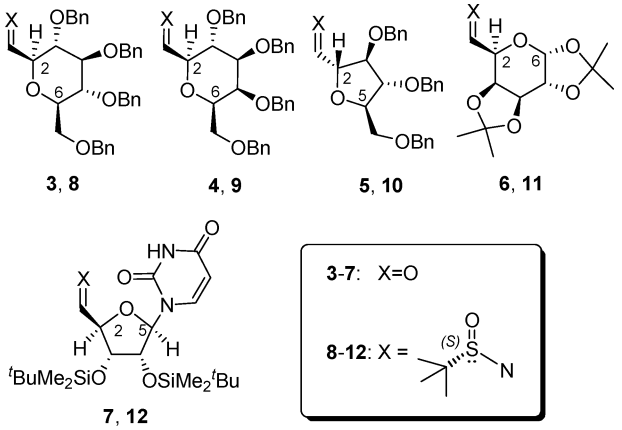


FIGURE 1. *C*-Glycosyl aldehydes **3**−**7** and their (S_S)-*N*-sulfinyl azomethines **8**−**12**.

TABLE 1. Reactions between Enolates 1a and 2a with Imines 8−**12**

entry	imine	enolate	product[a]	yield (%)[b]	dr[c] (%)[d]
1	(*S*)-**8**	**1a**	(S_S,2*S*,5*S*,1′*R*)-**13**	91	>95
2	(*S*)-**8**	**2a**	(S_S,2*S*,5*R*,1′*S*)-**14**	88	>95
3	(*S*)-**9**	**1a**	(S_S,2*S*,5*R*,1′*R*)-**15**	89	>95
4	(*S*)-**9**	**2a**	(S_S,2*S*,5*R*,1′*S*)-**16**	87	>95
5	(*S*)-**10**	**1a**	(S_S,2*S*,5*R*,1′*R*)-**17**	58	>95
6	(*S*)-**10**	**2a**	(S_S,2*S*,5*R*,1′*R*)-**18**	80	>95
7	(*S*)-**11**	**1a**	(S_S,2*S*,5*R*,1′*R*)-**19** + (S_S,2*S*,5*R*,1′*S*)-**20**	83	90
8	(*S*)-**11**	**2a**	(S_S,2*S*,5*R*,1′*R*)-**21** + (S_S,2*S*,5*R*,1′*S*)-**22**	58[e]	0
9	(*S*)-**12**	**1a**	(S_S,2*S*,5*R*,1′*R*)-**23**	87	>95
10	(*S*)-**12**	**2a**	(S_S,2*S*,5*R*,1′*S*)-**24**	88	>95

[a] R = (*S*)-S(O)^{t}Bu; R^1 = ^{t}BuMe$_2$Si. [b] Major isomer isolated yields. [c] Diastereomeric ratio between the (2*S*,5*R*,1′*R*)- and the (2*S*,5*R*,1′*S*)-isomers. [d] Determined by ^{1}HNMR analysis of the crude compound. [e] Isolated yield of the diastereomeric mixture.

partners. Dioxolanone (2*S*,5*S*)-**1** was obtained by acetalization of (*S*)-lactic acid with pinacolone with 98 de,[34] while dioxolanone (2*S*,5*S*)-**2**, which bears a more steric demanding phenyl group at C-5 position, was synthesized as homochiral material by acetalization of (*S*)-mandelic acid with pivalaldehyde.[28,35] The chiral enolate precursors, namely (*S*)-α-hydroxy acids, are available from the chiral pool, while their (*R*)-enantiomers can be easily obtained from (*R*)-α-amino acids following simple literature procedures.[35] This feature ensures a variety of substituents at the C2 stereogenic center of the resulting isoserine (R, Scheme 2).

Treatment of **1** and **2** with lithium (bis) trimethylsilyl amide gave the nonracemic (2*S*)-lithium enolates **1a** and **2a**, respectively. Reactions between the enolates and the imines were carried out in a 85:15 THF/HMPA mixed solvent at −78/−90 °C and required an excess of lithium enolate (3.2−3.8 equiv) to ensure a complete consumption of the sugar imine. To minimize imine oligomerization and undesired side reactions,

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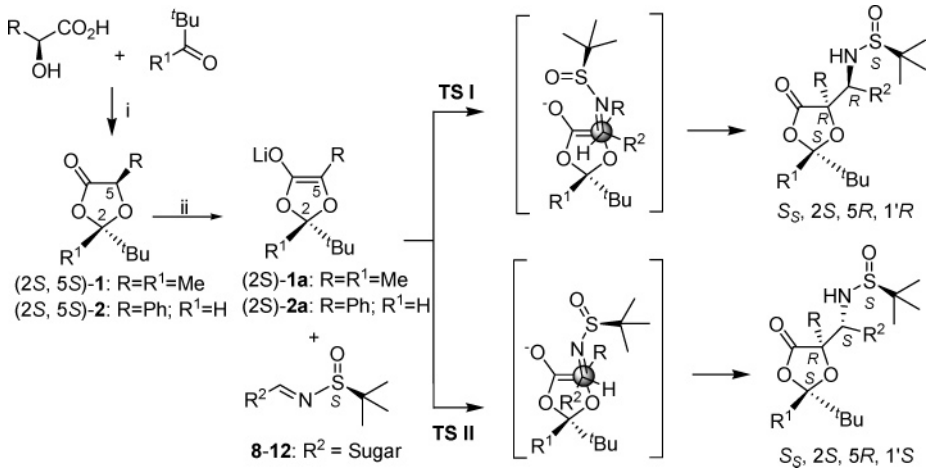
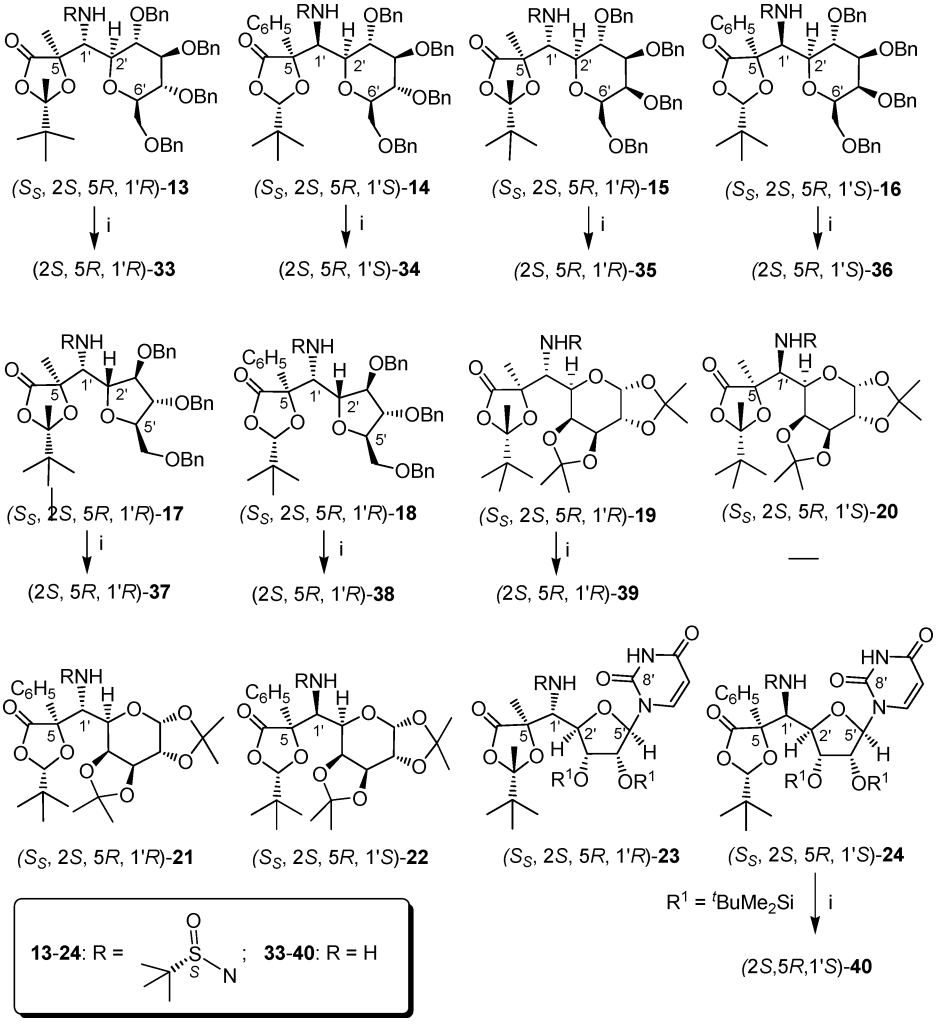
SCHEME 2. Synthesis of (S_S)-1′-Sulfinylaminodioxolanones[a]



[a] Reagents and conditions: (i) *p*-toluenesulfonic acid (PTSA); (ii) LHMDS, THF/HMPA, −78 °C.

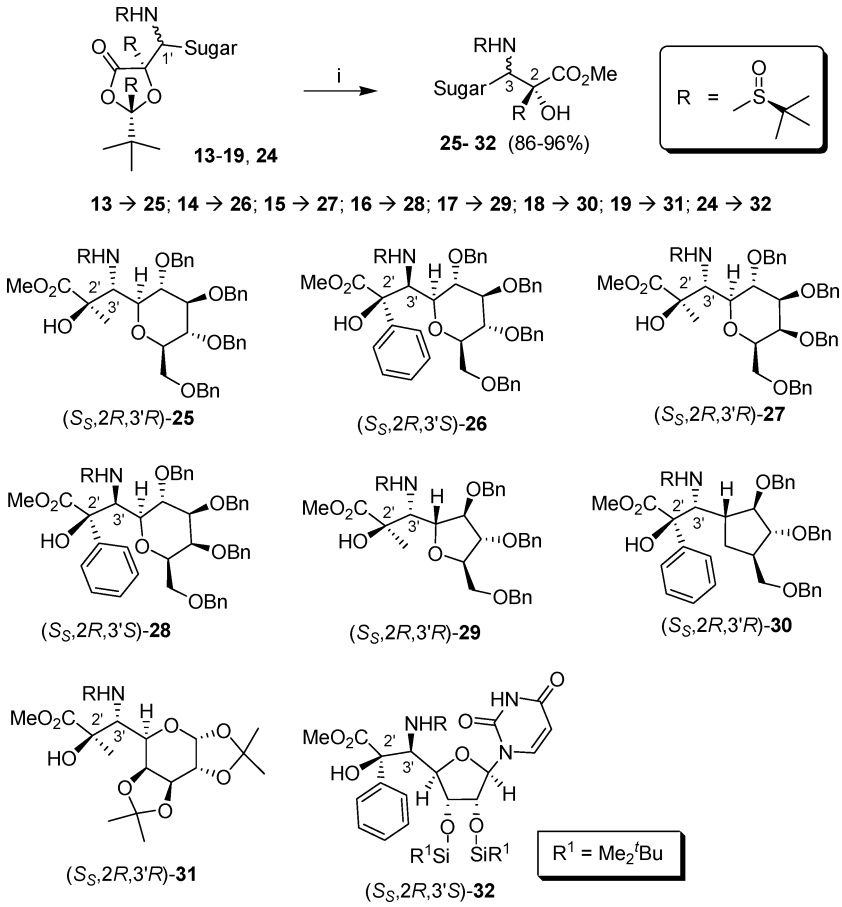
SCHEME 3. Chemical Correlation between (S_S)-1′-Sulfinylaminodioxolanones 13−24 and N-Deprotected 1′-Aminodioxolanones 33−40[a]



[a] Reagents and conditions: (i) 2 N HCl in 1:1 MeOH/Et_2O.

the addition to enolates needed to be very slow. The reaction afforded the 1′-sulfinylamino-dioxolanones **13**−**24** (Table 1, Scheme 3) with moderate to good overall yields (58−91%), and the regioselectivity of the reaction was governed by Seebach's "self-regeneration of stereocenters" synthetic principle (SRS). Namely, the imine approaches the chiral (2*S*)-enolate

SCHEME 4. Synthesis of Methyl Isoserinates 25−32 from (S_S)-1′-Sulfinylaminodioxolanones 13−19 and 24[a]



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

from its less hindered face which bears a methyl (**1a**) or a hydrogen atom (**2a**) at the acetal center. Accordingly, only the isomers with 5*R* stereochemistry [(2*S*,5*R*,1′*R*) and/or (2*S*,5*R*,1′*S*)] were formed.

The presence of isomers with 5*S*-stereochemistry was not observed on a ^{1}H NMR scale (400 MHz). It is worth noting that all reactions were highly diastereoselective with exception of entry 8 which gave a 1:1 mixture of epimers **21** and **22**. The stereochemistry at the 1′ position strongly depends on reagents steric requirements. When enolate **1a** was used as a reaction partner, the selectivity was directed by the small methyl substituent at the C-5 carbon atom of the enolate, which favored an exo approach of the imine to the dioxolanone ring according to TS I (Scheme 2).

As the consequence, the (2*S*,5*R*,1′*R*)-isomers **13**, **15**, **17**, **19**, and **23** were formed with high de (≥90%), especially when bulky benzyl or *tert*-butyldimethylsilyl substituents were present on the sugar ring (Table 1). On the other hand, when the enolate **2a**, which bears the more steric demanding phenyl group at C5 and the smaller hydrogen atom at C2, was employed the diastereofacial selectivity strongly depended on the type of sugar residue. For instance, the β-D-glucosyl, β-D-galactosyl, and the nucleoside azomethines **8**, **9**, and **12** only afforded the 1′*S*-epimers, **14**, **16**, and **24**, while the α-D-arabinose azomethine **10** afforded 1′*R*-epimer **18** as a sole diastereoisomer, and the -α-D-galactohexo-dialdo-1,5-pyranose azomethine **11** gave a 1:1 mixture of **21**/**22**. From these observations, it appears that the sugar residue plays an important and rather complex role on the stereochemical outcome when the enolate **2a** is the reaction partner which is hard to rationalize by simple classical steric models.[36]

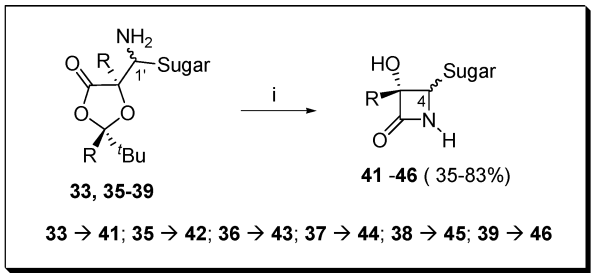
Sulfinyl deprotection of **13**−**19** and **24** with 2 N HCl afforded the 1′amino-dioxolanones **33**−**40** (Scheme 3), while the selective removal of the acetal group of **13**−**19** and **24** was carried out under basic conditions providing the methyl isoserinates **25**−**32** (Scheme 4), thus probing the orthogonality of the acetal group and *N*-sulfinyl substituent. Accordingly, these heterocycles can be directly susceptible to further peptide coupling reactions avoiding tedious protection/deprotection steps.

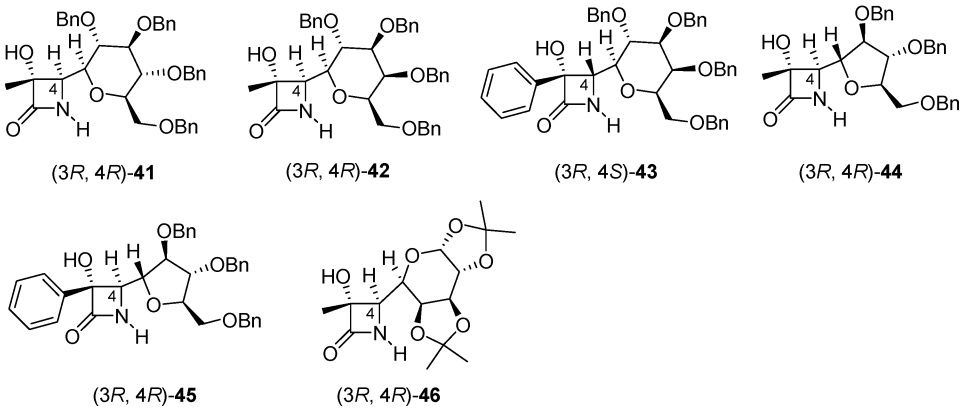
LHMDS induced cyclization of the *N*-deprotected 1′-amino-dioxolanones **33** and **35**−**39** yielded the β-lactams **41**−**46** (Scheme 5).

Nuclear Overhauser effect (NOE) experiments allowed us to assign the absolute configuration of the 1′-sulfinylamino dioxolanones (2*S*,5*R*,1′*R*)-**23** and (2*S*,5*R*,1′*S*)-**24**. These experiments showed that compound **24** adopts a restricted (1′*S*)-conformation, as represented in Figure 2. In this conformation, significant NOEs (3−4%) were observed between the ortho aromatic protons of the C5 phenyl substituent (7.92 ppm) and the ^{t}Bu group attached to the sulfur atom, the H1′ proton (3%), and the NH group (3%). Moreover, this conformation was further confirmed by the presence of a relevant NOE between H2 and H2′ and by the absence of it between the H6′ and H7′ (uridine moiety) with the following substituents: NH, H1′, H2, and ^{t}BuS-

(36) For a review, see Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191.

SCHEME 5. Synthesis of β-Lactams 41−46 from 1′-Aminodioxolanones 33, and 35−39[a]

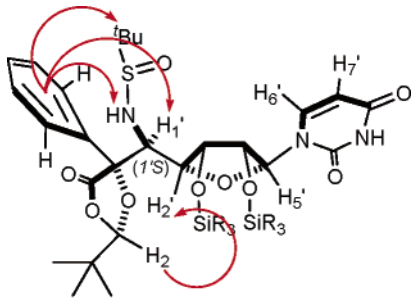




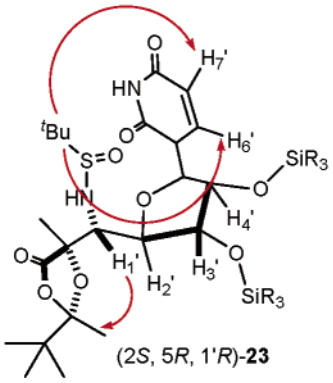
[a] Reagents and conditions: (i) LHMDS/THF.

(O). A quite different behavior was observed with (2*S*,5*R*,1′*R*)-**23**, whose conformation was assessed by X-ray spectroscopy (see Supporting Information).

As shown in Figure 2 (compound **23)**, no NOE was detected between the *t*butyl group attached to the sulfur atom and the methyl group at C5, while a relevant NOE was found between the same *t*butyl group and the H6′ (7.44 ppm, 1%) and H7′ (5.77 ppm, 2%) protons of the uridine moiety. Consistently, a strong NOE was observed between the C2-Me group at 1.51 ppm and H1′ (3.59 ppm, 8%). Moreover, X-ray spectroscopy allowed the stereochemical assignment of the *C*-glycosyl methyl isoserinate derivative (2*R*,3*S*)-**26**, thus confirming the stereochemistry of (2*S*,5*R*,1′*S*)-**24** (see Supporting Information). NOE experiments also allowed us to assign the stereochemistry of the β-lactams **41**−**46**, thus of their chemically correlated derivatives (Schemes 3−5).



(2*S*, 5*R*, 1′*S*)-**24**



(2*S*, 5*R*, 1′*R*)-**23**

FIGURE 2. NOE experiments on 1′-sulfinylamino dioxolanones (2*S*,5*R*,1′*R*)-**23** and (2*S*,5*R*,1′*S*)-**24**.

Conclusions

A very efficient and stereoselective method for the incorporation of a carbohydrate-based five- or six-membered scaffolds into the side chain of conformationally constrained chiral α-hydroxy-$\beta^{2,2,3}$-amino acids is reported. In particular, for the first time the synthesis of nucleoside norstatines is presented. As a general rule, the stereochemical outcome of the reaction strongly depends on the size of the C2 substituent of the α-hydroxy acid. Namely, anti isomers, derived from TS I, are preferred with dioxolanone **1**, while syn isomers, derived from TS II, are favored when dioxolanone **2** is employed. Furthermore, the chirality of the quaternary C2 stereogenic center of the resulting *C*-glycosyl isoserine is governed by the chirality of the α-hydroxy acid reagent: The stereochemical relationship between the C2 carbon atom of the isoserine and that of the α-hydroxy acid occurs with an inversion of configuration.

Finally, the imine/ester enolate and the ketene/imine protocols are complementary when conformational constrained 2-methylisoserines are the reaction targets. In fact, Staudinger's protocol is currently used for synthesis of syn C3, C4-disubstituted

3-hydroxy-β-lactams as precursors of the corresponding syn α-hydroxy-β-amino acids,[19] while our protocol affords their anti-isomers.

Experimental Section

General Procedure for Synthesis of *N*-Sulfinyl Aldimines. The synthesis of enantiomerically (*S*)-*N*-*tert*-butanesulfinyl imines was performed by the direct condensation of (*S*)-*tert*-butanesulfinamide with the corresponding aldehydes according to a slightly modified literature procedure.[9b] A solution of the aldehyde (1.0 equiv) in CH_2Cl_2 (10 mL × 1.0 mmol) was reacted with (*S*)-*tert*-butanesulfinyl imine (1.15 equiv) in the presence of 5.0 equiv of anhydrous $MgSO_4$ and 0.05 equiv of *p*-toluenesulfinic acid (PPTS) as the catalyst. The reaction mixture was stirred at 20 °C and filtered through a Celite pad. The Celite was washed several times with CH_2Cl_2, and the combined organic phases were concentrated under reduced pressure. The residue was purified by silica gel column chromatography. Imines (*S*)-**10** and (*S*)-**11** were obtained slightly contaminated by impurities but were used without further purification.

2-Methyl-*N*-{(1*E*)-[(2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-tribenzyloxy-6-(benzyloxymethyl)tetrahydro-2*H*-pyran-2-yl]methylene}propane-2-sulfinamide (*S*)-8. The aldehyde **3** (1.050 g, 1.91 mmol) was reacted with (*S*)-*tert*-butanesulfinyl amide (0.31 g, 1.91 mmol) in the presence of 1.15 g of $MgSO_4$ and 0.016 g of PPTS at 20 °C for 24 h. Chromatography (SiO_2, *n*-hexane/EtOAc, 5:1) yielded compound **8** (0.81 g, 1.24 mmol, 65%): $[\alpha]^{20}_D = -92.0$ (*c* 0.6, $CHCl_3$). IR (Nujol, cm^{-1}): 1611, 1082. MS (*m*/*z*): 656 $(M + 1)^+$, 551, 458, 352, 181. HRMS *m*/*z* calcd for $C_{39}H_{46}NO_6S$ $[M + 1]^+$, 656.3046; *m*/*z* found, 656.3033. ^1H NMR (C_6D_6): δ 8.39 (d, 1H, $J = 4.8$ Hz, CH═N), 7.30−7.00 (m, 20H, arom), 4.82 (d, 1H, $J = 10.8$ Hz), 4.76 (d, 1H, $J = 10.8$ Hz), 4.75 (d, 1H, $J = 11.2$ Hz), 4.60 (d, 1H, $J = 11.6$ Hz), 4.48 (d, 1H, $J = 11.2$ Hz), 4.44 (d, 1H, $J = 12.0$ Hz), 4.35 (d, 1H, $J = 12.0$ Hz), 3.98 (dd, 1H, J_1=4.8 Hz, J_2=9.6 Hz), 3.73 (t, 1H, $J = 9.2$ Hz), 3.66−3.50 (m, 4H), 3.34−3.26 (m, 1H), 1.36 (s, 3H, Me), 0.97 (s, 9H, 3 Me). ^{13}C NMR (C_6D_6): δ 165.1, 139.1, 138.9, 138.8, 138.5, 128.5−127.5, 87.0, 79.9, 79.8, 79.4, 78.1, 75.4, 74.9, 74.6, 73.6, 68.9, 57.1, 22.2. Anal. Calcd for $C_{39}H_{45}NO_6S$: C, 71.42; H, 6.92; N, 2.14. Found: C, 71.23; H, 6.85; N, 2.20.

***N*-{(1*E*)-[(2*S*,3*S*,4*R*,5*S*,6*R*)-3,4,5-Tribenzyloxy-6-(benzyloxymethyl)tetrahydro-2*H*-pyran-2-yl]methylene}-*tert*-butanesulfinamide (*S*)-9.** The aldehyde **4** (0.90 g, 1.64 mmol) was reacted with (*S*)-*tert*-butanesulfinyl amide (0.23 g, 1.89 mmol) in the presence of 0.99 g of $MgSO_4$ and 0.014 g of PPTS at 20 °C for 24 h. Chromatography (SiO_2, *n*-hexane/EtOAc, 5:1) yielded compound **8** (0.90 g, 1.37 mmol, 72%): $[\alpha]^{20}_D$ +96.0 (c 0.3, $CHCl_3$). IR (Nujol, cm^{-1}): 2868, 1629, 1452, 1088. MS (*m*/*z*): 550 $(M-S(O)^tBu)^+$, 458, 352, 287, 181, 91. HRMS *m*/*z* calcd for $C_{39}H_{46}NO_6S$ $[M + 1]^+$, 656.3046; *m*/*z* found, 656.3038. ^1H NMR ($CDCl_3$): δ 8.10 (d, 1H, $J = 4.5$ Hz, CH═N), 7.35−7.00 (m, 20H, arom), 4.95 (dd, 1H, J_1=4.4 Hz, J_2=10.8 Hz), 4.76 (d, 1H, $J = 11.6$ Hz), 4.70 (d, 1H, $J = 11.6$ Hz), 4.63 (d, 1H, $J = 8.4$ Hz), 4.60 (d, 1H, $J = 8.4$ Hz), 4.48 (d, 1H, $J = 12.0$ Hz), 4.43 (d, 1H, $J = 12.0$ Hz), 4.12 (d, 1H, $J = 10.4$ Hz), 4.10 (d, 1H, $J = 2.0$ Hz), 4.08 (d, 1H, $J = 10.4$ Hz), 4.02 (d, 1H, $J = 12.0$ Hz), 3.74−3.58 (m, 4H), 1.14 (s, 9H, 3Me). ^{13}C NMR ($CDCl_3$): δ 165.2, 138.2, 138.2, 138.1, 138.0, 128.7−127.8, 84.8, 77.7, 77.5, 76.2, 75.2, 74.8, 73.8, 73.6, 72.5, 68.9, 57.3, 22.6. Anal. Calcd for $C_{39}H_{45}NO_6S$: C, 71.42; H, 6.92; N, 2.14. Found: C, 71.23; H, 6.95; N, 2.22.

***N*-{(1*E*)-[(2*R*,3*R*,4*R*,5*R*)-3,4-Dibenzyloxy-5-(benzyloxymethyl)tetrahydrofuran-2-yl]methylene}-2-*tert*-butanesulfinamide (*S*)-10.** The aldehyde **5** (0.97 g, 2.24 mmol) was reacted with (*S*)-*tert*-butanesulfinyl amide (0.31 g, 2.58 mmol) in the presence of 1.35 g of $MgSO_4$ and 0.019 g of PPTS at 20 °C for 18 h. Chromatography (SiO_2, *n*-hexane/EtOAc, 5:1) yielded compound **10** (0.92 g, 1.72 mmol, 77%). IR (Nujol, cm^{-1}): 1624, 1458, 1085. MS (*m*/*z*): 535 $(M)^+$, 478, 430, 323. HRMS *m*/*z* calcd for $C_{31}H_{37}NO_5S$ $[M]^+$, 535.2392; *m*/*z* found, 535.2388. ^1H NMR ($CDCl_3$): δ 8.08 (d, 1H, $J = 3.6$ Hz, CH═N), 7.35−7.20 (m, 15H, arom), 4.88 (m, 1H, H3′), 4.58−4.46 (m, 6H, $3CH_2$), 4.32 (m, 1H, H5′), 4.22 (m, 1H, H2′), 4.09 (dd, 1H, J_1=2.4 Hz, J_2=4.4 Hz, H4′), 3.66−3.58 (m, 2H, CH_2), 1.19 (s, 9H, 3Me). ^{13}C NMR ($CDCl_3$): δ 167.5, 138.0−137.4, 128.5−127.7, 86.2, 84.5, 83.9, 83.0, 73.4, 72.0, 71.8, 69.8, 57.6, 22.4. Anal. Calcd for $C_{31}H_{37}NO_5S$: C, 69.50; H, 6.96; N, 2.61. Found: C, 69.33; H, 6.85; N, 2.70.

N-{(1*E*)-[(3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-2,2,7,7-Tetramethyltetrahydro-3a*H*-*bis*[1,3]dioxolo[4,5-b:4′,5′-d]pyran-5-yl]methylene}*tert*-butanesulfinamide (*S*)-11. The aldehyde **6** (0.80 g, 3.10 mmol) was reacted with (*S*)-*tert*-butanesulfinyl amide (0.43 g, 3.57 mmol) in the presence of 1.87 g of $MgSO_4$ and 0.027 g of PPTS at 20 °C for 24 h. Chromatography (SiO_2, *n*-hexane/EtOAc, 5:1) yielded compound **10** (0.76 g, 2.11 mmol, 68%): IR (Nujol, cm^{-1}): 1624, 1087. MS (*m*/*z*): 361 $(M)^+$, 256. HRMS *m*/*z* calcd for $C_{16}H_{27}NO_6S$ $[M]^+$, 361.1559; *m*/*z* found, 361.1570. ^1H NMR ($CDCl_3$): δ 7.98 (d, 1H, $J = 3.2$ Hz, CH═N), 5.61 (d, 1H, $J = 4.8$ Hz), 4.68−4.56 (m, 2H), 4.48 (dd, 1H, J_1=2.0 Hz, J_2=8.0 Hz); 4.35 (dd, 1H, J_1=2.4 Hz, J_2=5.2 Hz), 1.50 (s, 3H, Me), 1.39 (s, 3H, Me), 1.32 (s, 3H, Me), 1.28 (s, 3H, Me), 1.19 (s, 9H, 3Me). ^{13}C NMR ($CDCl_3$): δ 165.6, 110.1, 109.1, 96.6, 72.3, 70.9 (2 CH−O), 70.6, 57.6, 26.3, 26.1, 25.1, 24.6, 22.7. Anal. Calcd for $C_{16}H_{27}NO_6S$: C, 53.17; H, 7.53; N, 3.88. Found: C, 53.03; H, 7.65; N, 3.95.

(5-*tert*-Butylsulfinyliminomethyl)-2′,3′-di-*tert*-butyldimethylsilyl-uridine (*S*)-12. The aldehyde **7** (1.01 g, 2.12 mmol) was reacted with (*S*)-*tert*-butanesulfinyl amide (0.32 g, 2.65 mmol) in the presence of 1.28 g of $MgSO_4$ and 0.018 g of PPTS at 20 °C for 24 h. Silica gel column chromatography (eluent: EtOAc/hexane 1/2) afforded the pure compound **12** as a white solid in 80% yield: $[\alpha]^{20}_D$ +137.2 (c 0.25, $CHCl_3$): IR (Nujol, cm^{-1}): 2928, 2355, 1693, 1254, 1082. MS (*m*/*z*): 574 $(M)^+$, 468, 458, 343. HRMS *m*/*z* calcd for $C_{25}H_{47}N_3O_6SSi_2$ $[M]^+$, 573.2724; *m*/*z* found, 573.2711. ^1H NMR ($CDCl_3$): δ 9.65 (b, 1H, NH), 8.16 (d, 1H, $J = 3.2$ Hz), 7.81 (d, 1H, $J = 8.0$ Hz), 5.87 (d, 1H, $J = 4.4$ Hz), 5.70 (d, 1H, $J = 8.0$ Hz), 4.87 (dd, 1H, J_1=3.2 Hz, J_2=4.8 Hz), 4.10−4.06 (m, 2H), 1.23 (s, 9H 3Me), 0.90 (s, 9H, 3Me), 0.87 (s, 9H 3Me), 0.07 (s, 3H, Me), 0.06 (s, 3H, Me), 0.04 (s, 3H, Me), 0.03 (s, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 166.3, 163.4, 150.1, 140.1, 102.4, 90.5, 84.6, 74.9, 74.3, 57.2, 25.7, 25.6, 25.6, 22.3, 18.0, 17.9, −4.4, −4.8, −4.9, −5.0. Anal. Calcd for $C_{25}H_{47}N_3O_6SSi_2$: C, 52.32; H, 8.25; N, 7.32. Found: C, 52.46; H, 8.32; N, 7.29.

General Procedure for Synthesis of *N*-Sulfinyl 1′-Aminodioxolanones. Unless otherwise stated, a THF solution of dioxolanone was added dropwise at −78 °C to a solution of LHMDS in THF. The solution was stirred at −70 °C for 1 h and then cooled to −90 °C. A HMPA/THF solution was then added dropwise, and after 5 min a THF solution of the *N*-sulfinyl azomethine was introduced by syringe pump at the rate of 1.0 mL/hour, in a temperature range of −85 to −78 °C. After complete addition, the temperature was raised to −60 °C during 1 h, and the mixture was stirred for an additional 30 min. The crude material was obtained according to the following standard workup: The reaction was quenched by the addition of 0.1 N HCl at −60 °C and then warmed to room temperature. The crude reaction mixture was extracted three times with EtOAc, and the combined organic phases were washed three times with 0.1 N HCl, followed by saturated NH_4Cl. The organic phase was dried over Na_2SO_4, filtered, and then concentrated under vacuum. Silica gel column chromatography afforded the desired compounds.

(2*S*,5*R*,1′*R*)-13. The dioxolanone (2*S*,5*S*)-**1** (0.12 g, 0.71 mmol) was reacted with imine (*S*)-**8** (0.14 g, 0.22 mmol). Silica gel column chromatography of the crude compound (*n*-hexane/EtOAc, 7:3) afforded (2*S*,5*R*,1′*R*)-**13** (0.16 g, 0.20 mmol, 90%): $[\alpha]^{20}_D$ +52.1 (c 0.8, $CHCl_3$). IR (Nujol, cm^{-1}): 2961, 1793, 1453, 1365, 1151, 1068. MS *m*/*z* 828 $(M)^+$, 552, 488, 444, 181. HRMS *m*/*z* calcd for $C_{48}H_{61}NO_9SNa$ $[M + Na]^+$, 850.3965; *m*/*z* found, 850.3981. ^1H NMR ($CDCl_3$, $T = 58$ °C): δ 7.40−7.10 (m, 20H, arom), 5.23 (d, 1H, $J = 12.5$ Hz), 4.97 (d, 1H, $J = 11.0$ Hz), 4.81 (d, 1H, $J =$

12.5 Hz), 4.78 (d, 1H, J = 11.0 Hz), 4.70 (d, 1H, J = 11.0 Hz), 4.59 (d, 1H, J = 11.0 Hz), 4.55 (d, 1H, J = 11.6 Hz), 4.49 (d, 1H, J = 11.6 Hz), 4.15 (dd, 1H, J_1=8.5 Hz, J = 10.0 Hz, H3′), 4.10 (d, 1H, J = 10.0 Hz, NH), 3.92 (dd, 1H, J_1=3.0 Hz, J_2=10.0 Hz, H1′), 3.84 (dd, 1H, J_1=3.0 Hz, J_2=10.0 Hz, H2′), 3.80 (t, 1H, J = 8.5 Hz, H4′), 3.70−3.62 (m, 3H, 2H of CH_2 and 1H of H5′), 3.51 (dt, 1H, J_1=3.2 Hz, J_2=9.6 Hz, H6′), 1.44 (s, 3H, Me), 1.37 (s, 3H, Me), 1.18 (s, 9H, 3Me), 0.93 (s, 9H, 3Me). ^{13}C NMR ($CDCl_3$): δ 172.9, 138.9, 138.5, 138.4, 138.2, 128.7, 128.6, 128.6, 128.5, 128.1, 128.0, 127.8, 127.7, 127.6, 127.4, 126.2, 114.5, 88.2, 80.2, 79.3, 79.1, 78.8, 77.5, 75.1, 75.0, 73.5, 72.1, 69.4, 64.6, 57.1, 39.2, 24.9, 23.0, 22.6, 20.1. Anal. Calcd for $C_{48}H_{61}NO_9S$: C, 69.62; H, 7.43; N, 1.69. Found: C, 69.43; H, 7.51; N, 1.65.

(2*S*,5*R*,1′*S*)-14. The dioxolanone (2*S*,5*S*)-**2** (0.16 g, 0.73 mmol) was reacted with imine (*S*)-**8** (0.15 g, 0.23 mmol). Silica gel column chromatography of the crude compound (*n*-hexane/EtOAc, 7:3) afforded (2*S*,5*R*,1′*S*)-**14** (0.17 g, 0.20 mmol, 88%): $[\alpha]^{20}_D$ −2.9 (c 0.40, $CHCl_3$). IR (Nujol, cm^{-1}): 2869, 1788, 1452, 1363, 1071. MS (*m*/*z*): 773 (M − Me_3HCO_2)$^+$, 656, 551, 181, 105. HRMS *m*/*z* calcd for $C_{52}H_{61}NO_9S$ [M]$^+$, 875.4067; *m*/*z* found, 875.4054. ^{1}H NMR ($CDCl_3$): δ 7.75−7.65 (m, 2H, arom), 7.40−7.20 (m, 23H, arom), 5.39 (s, 1H, O−C*H*-O), 4.87 (d, 2H, J = 11.2 Hz), 4.81 (d, 2H, J = 11.2 Hz), 4.65 (m, 2H), 4.60 (d, 1H, J = 10.8 Hz), 4.57 (d, 1H, J = 12.0 Hz), 4.49 (d, 1H, J = 12.0 Hz), 4.18 (dd, 1H, J_1=0.8 Hz, J_2=10.4 Hz), 3.77 (dd, 1H, J_1=3.2 Hz, J_2=11.2 Hz), 3.60−3.57 (m, 2H), 3.55 (dd, 1H, J_1=2.0 Hz, J_2=11.2 Hz), 3.57−3.46 (m, 1H), 3.37 (dd, 1H, J_1=0.8 Hz, J_2=9.2 Hz), 3.20 (m, 1H), 1.23 (s, 9H, 3Me), 0.87 (s, 9H, 3Me). ^{13}C NMR ($CDCl_3$): relevant resonances at δ 172.7, 138.8, 138.5, 138.3, 138.1, 136.8, 128.9−126.2, 110.7 (O−CH−O), 87.5, 79.2, 78.2, 77.6, 77.3, 76.9, 76.0, 75.3, 75.1, 73.9, 68.9, 61.4, 57.6, 35.4, 23.9, 23.4. Anal. Calcd for $C_{52}H_{61}NO_9S$: C, 71.29; H, 7.02; N, 1.60. Found: C, 71.06; H, 7.15; N, 1.55.

(2*S*,5*R*,1′*R*)-15. The dioxolanone (2*S*,5*S*)-**1** (0.14 g, 0.83 mmol) was reacted with imine (*S*)-**9** (0.17 g, 0.26 mmol). Silica gel column chromatography of the crude compound (*n*-hexane/EtOAc, 7:3) afforded (2*S*,5*R*,1′*R*)-**15** (0.169 g, 0.20 mmol, 89%): $[\alpha]^{20}_D$ +31.5 (c 0.5, $CHCl_3$). IR (Nujol, cm^{-1}): 2962, 1790, 1454, 1281, 1082. MS *m*/*z* 828 (M)$^+$, 680, 552, 488, 444, 354, 181. HRMS *m*/*z* calcd for $C_{48}H_{61}NO_9S$ [M]$^+$, 827.4067; *m*/*z* found, 827.4078. ^{1}H NMR ($CDCl_3$): δ 7.40−7.10 (m, 20H, arom), 5.28 (d, 1H, J = 13.0 Hz), 4.99 (d, 1H, J = 11.5 Hz), 4.82 (d, 1H, J = 13.0 Hz), 4.71 (d, 1H, J = 11.5 Hz), 4.59 (d, 1H, J = 11.5 Hz), 4.52 (d, 1H, J = 11.5 Hz), 4.46 (d, 1H, J = 12.0 Hz), 4.43 (d, 1H, J = 12.0 Hz), 4.36 (t, 1H, J = 6.0 Hz), 4.29 (d, 1H, J = 10.0 Hz), 4.02 (dd, 1H, J_1=3.2 Hz, J_2=10.0 Hz), 3.99 (d, 1H, J = 2.0 Hz), 3.85 (dd, 1H, J_1=3.2 Hz, J_2=10.0 Hz), 3.67 (dd, 1H, J_1=2.0 Hz, J_2=8.8 Hz), 3.68−3.50 (m, 3H, 2H of CH_2 and 1 CH), 1.53 (s, 3H, Me), 1.31 (s, 3H, Me), 1.20 (s, 9H, 3Me), 0.95 (s, 9H, 3Me). ^{13}C NMR ($CDCl_3$): relevant resonances at δ 172.7, 136.6, 139.1, 138.1, 137.9, 128.7−125.9, 114.4, 86.3, 81.3, 81.2, 77.0, 74.5, 73.6, 73.4, 72.3, 72.0, 69.3, 61.8, 57.0, 39.3, 24.9, 22.9, 22.8, 20.6. Anal. Calcd for $C_{48}H_{61}NO_9S$: C, 69.62; H, 7.43; N, 1.69. Found: C, 69.58; H, 7.35; N, 1.60.

(2*S*,5*R*,1′*S*)-16. The dioxolanone (2*S*,5*S*)-**2** (0.20 g, 0.91 mmol) was reacted with imine (*S*)-**9** (0.19 g, 0.28 mmol). Silica gel column chromatography of the crude compound (*n*-hexane/EtOAc, 7:3) afforded (2*S*,5*R*,1′*S*)-**16** (0.17 g, 0.20 mmol, 87%): $[\alpha]^{20}_D$ −1.1 (c 2.0, $CHCl_3$). IR (Nujol, cm^{-1}): 2864, 1784, 1455, 1363,1065. MS (*m*/*z*): 875 (M),$^+$ 656, 551, 181, 105. HRMS *m*/*z* calcd for $C_{52}H_{61}NO_9S$ [M]$^+$, 875.4067; *m*/*z* found, 875.4080. ^{1}H NMR ($CDCl_3$): δ 7.65−7.60 (m, 2H, arom), 7.40−7.10 (m, 18H, arom), 5.33 (s, 1H, O−CH−O), 4.91 (d, 1H, J = 11.0 Hz), 4.86 (d, 1H, J = 11.0 Hz, CH), 4.74 (d, 1H, J = 12.0 Hz), 4.63 (d, 1H, J = 12.0 Hz), 4.62 (d, 1H, J = 11.0 Hz), 4.54 (d, 1H, J = 10.5 Hz), 4.53 (d, 1H, J = 12.0 Hz), 4.47 (d, 1H, J = 11.0 Hz), 4.47 (d, 1H, J = 12.0 Hz), 4.17 (d, 1H, J = 10.5 Hz, H1′), 3.93 (t, 1H, J = 9.0 Hz, H3′), 3.93 (d, 1H, J = 2.0 Hz, H5′), 3.59 (dd, 1H of CH_2, J_1=7.5 Hz, J_2=9.0 Hz), 3.53 (dd, 1H, J_1=2.0 Hz, J_2=9.0 Hz, H4′), 3.44 (dd, 1H, J_1=5.0 Hz, J_2=9.0 Hz, H of CH_2), 3.42 (d, 1H, J_2=9.0 Hz, H2′), 3.38 (dd, 1H, J_1=5.0 Hz, J_2 =7.5 Hz, H6′), 1.08 (s, 9H, 3Me), 0.83 (s, 9H, 3Me). ^{13}C NMR ($CDCl_3$): relevant resonances at δ 172.7, 138.9, 138.5, 138.3, 138.1, 136.9, 128.8−126.3, 110.5, 85.1, 82.6, 77.1, 76.6, 75.3, 75.0, 74.6, 73.8 (2 CH_2), 72.2, 68.6, 62.0, 57.6, 35.4, 23.8, 23.2. Anal. Calcd for $C_{52}H_{61}NO_9S$: C, 71.29; H, 7.02; N, 1.60. Found: C, 71.49; H, 7.13; N, 1.51.

(2*S*,5*R*,1′*R*)-17. The dioxolanone (2*S*,5*S*)-**1 (**0.14 g, 0.83 mmol) was reacted with the imine (*S*)-**9** (0.17 g, 0.26 mmol). Silica gel column chromatography of the crude compound (*n*-hexane/EtOAc, 7:3) afforded (2*S*,5*R*,1′*R*)-**17** (0.11 g, 0.13 mmol, 58%): $[\alpha]^{20}_D$ +52.1 (c 0.8, $CHCl_3$). IR (Nujol, cm^{-1}): 2961, 1793, 1453, 1365, 1151, 1068. MS *m*/*z* 708 (M)$^+$, 560, 503, 432, 181. HRMS *m*/*z* calcd for $C_{40}H_{53}NO_8S$ [M]$^+$, 707.3492; *m*/*z* found, 707.3505. ^{1}H NMR ($CDCl_3$): δ 7.40−7.20 (m, 15H, arom), 4.72 (d, 1H, J = 11.2 Hz), 4.67 (d, 1H, J = 1.2 Hz), 4.62 (d, 1H, J = 12.0 Hz), 4.64−4.50 (m, 3H, 2H of CH_2 and 1H of H3′), 4.53 (d, 1H, J = 12.0 Hz), 4.43 (dd, 1H, J_1=0.8 Hz, J_2=7.6 Hz, H2′), 4.37 (d, 1H, J = 6.8 Hz, NH), 4.24 (m, 1H, H5′), 4.07 (t, 1H, J = 4.5 Hz, H4′), 3.65 (dd, 1H, J_1=0.8 Hz, J_2=6.8 Hz, H1′), 3.56 (dd, 1H of CH_2, J_1 =5.2 Hz, J_2=10.0 Hz), 3.52 (dd, 1H, J_1=5.6 Hz, J_2=10.8 Hz, of CH_2), 1.48 (s, 3H, Me), 1.40 (s, 3H, Me), 1.30 (s, 9H, 3 Me), 0.97 (s, 9H, 3 Me). ^{13}C NMR ($CDCl_3$): δ 172.8, 138.1, 138.0, 137.8, 128.3−127.5, 113.7, 84.1, 83.3, 82.4, 80.0, 78.2, 73.2, 71.6, 69.8, 59.3, 56.6, 39.2, 24.9, 23.0, 22.9, 18.1. Anal. Calcd for $C_{40}H_{53}NO_8S$: C, 67.87; H, 7.55; N, 1.98. Found: C, 67.94; H, 7.46; N, 1.90.

(2*S*,5*R*,1′*R*)-18. The dioxolanone (2*S*,5*S*)-**2** (0.19 g, 0.88 mmol) was reacted with the imine (*S*)-**9** (0.18 g, 0.27 mmol). Silica gel column chromatography of the crude compound (*n*-hexane/EtOAc, 7:3) afforded (2*S*,5*R*,1′*R*)-**18** (0.170 g, 0.22 mmol, 80%): $[\alpha]^{20}_D$ +62.8 (c 0.8, $CHCl_3$). IR (Nujol, cm^{-1}): 2981, 1794, 1375, 1254, 1071. MS (*m*/*z*): 756 (M)$^+$, 608, 536, 428, 372, 324, 236, 181. HRMS *m*/*z* calcd for $C_{44}H_{53}NO_8S$ [M]$^+$, 755.3492; *m*/*z* found, 755.3479. ^{1}H NMR ($CDCl_3$): δ 7.85−7.80 (m, 2H, arom), 7.40−7.20 (m, 18H, arom), 5.59 (s, 1H, O−C*H*-O), 4.63 (d, 1H, J = 11.5 Hz), 4.60 (d, 1H, J = 11.5 Hz), 4.58−4.54 (m, 5H, 2CH_2 and 1H of H3′), 4.29 (d, 1H, J = 7.6 Hz, NH), 4.25 (m, 1H, H5′), 4.18 (dd, 1H, J_1=1.6 Hz, J_2=6.4 Hz, H2′), 3.96 (t, 1H, J = 4.0 Hz, H4′), 3.95 (dd, 1H, J_1=2.0 Hz, J_2=4.8 Hz, H1′), 3.50 (dd, 1H of CH_2, J_1=6.0 Hz, J_2=10.4 Hz), 3.46 (dd, 1H of CH_2, J_1=4.8 Hz, J_2=10.4 Hz), 1.00 (s, 9H, 3Me), 0.89 (s, 9H, 3Me). ^{13}C NMR ($CDCl_3$): δ 172.0, 138.6, 138.2, 138.1, 136.8, 128.6−127.8, 126.3, 110.0, 85.1, 84.8, 83.7, 82.3, 80.4, 73.6, 72.9, 71.8, 69.9, 62.0, 56.3, 35.4, 23.8, 22.9. Anal. Calcd for $C_{44}H_{53}NO_8S$: C, 69.91; H, 7.07; N, 1.85. Found: C, 69.73; H, 7.17; N, 1.75.

(2*S*,5*R*,1′*R*)-19 and (2*S*,5*R*,1′*S*)-20. The dioxolanone (2*S*,5*S*)-**1** (0.26 g, 1.52 mmol) was reacted with imine (*S*)-**11** (0.14 g, 0.40 mmol). Silica gel column chromatography of the crude compound (*n*-hexane/EtOAc, 11:9) afforded (2*S*,5*R*,1′*R*)-**19** (0.19 g, 0.35 mmol, 87%). [0.02 g of a 1.5:1 mixture of (2*S*,5*R*,1′*S*)-**20**/(2*S*,5*R*,1′*R*)-**19** was isolateted along with the major product]. (2*S*,5*R*,1′*R*)-**19**: $[\alpha]^{20}_D$ +16.1 (c 0.45, $CHCl_3$). IR (Nujol, cm^{-1}): 2981, 1794, 1375, 1254, 1084. MS (*m*/*z*): 534 (M + 1)$^+$, 349, 291, 172. HRMS *m*/*z* calcd for $C_{25}H_{44}NO_9S$ [M+1]$^+$, 534.2737; *m*/*z* found, 534.2736. ^{1}H NMR ($CDCl_3$): δ 5.59 (d, 1H, J = 4.8 Hz, H6′), 4.57 (dd, 1H, J_1=2.4, J_2=8.0 Hz, H4′), 4.48 (d, 1H, J = 3.2 Hz, NH), 4.32 (m, 1H, H2′), 4.30 (dd, 1H, J_1=1.6, J_2=8.0 Hz, H3′), 4.28 (dd, 1H, J_1=2.4 Hz, J_2=4.8 Hz, H5′), 3.88 (dd, 1H, J_1=2.5, J_2=3.2 Hz, H1′), 1.58 (s, 3H, Me), 1.57 (s, 3H, Me), 1.52 (s, 3H, Me), 1.48 (s, 3H, Me), 1.34 (s, 3H, Me), 1.33 (s, 3H, Me), 1.28 (s, 9H, 3Me), 0.97 (s, 9H, 3Me). ^{13}C NMR ($CDCl_3$): δ 172.6, 113.8, 110.0, 109.2, 97.1, 80.7, 74.1, 71.2, 71.0, 64.5, 57.9, 56.9, 39.3, 26.4, 26.0, 25.2, 24.8 (3 Me), 24.4, 23.5, 23.2 (3 Me), 18.0. Anal. Calcd for $C_{25}H_{43}NO_9S$: C, 56.26; H, 8.12; N, 2.62. Found: C, 56.43; H, 8.17; N, 2.55.

(2*S*,5*R*,1′*S*)-20. ^{1}H NMR ($CDCl_3$): δ 5.51 (d, 1H, J = 4.8 Hz, H6′), 5.15 (d, 1H, J = 9.2 Hz, NH), 4.66 (dd, 1H, J_1=1.0 Hz, J_2=8.4 Hz, H3′), 4.56 (dd, 1H, J_1=1.6, J_2=8.4 Hz, H4′), 4.25 (dd,

1H, J_1=1.6 Hz, J_2=4.8 Hz, H5′), 4.18 (dd, 1H, J_1=1.0 Hz, J_2=4.4 Hz, H2′), 3.96 (dd, 1H, J_1=4.4 Hz, J_2=9.2 Hz, H1′), 1.54 (s, 3H, Me), 1.49 (s, 6H, 2Me), 1,35 (s, 3H, Me), 1.33 (s, 6H, 2Me), 1.23 (s, 9H, 3Me), 1.02 (s, 9H, 3Me). ^{13}C NMR ($CDCl_3$): δ 173.9, 116.3, 109.1, 108.7, 96.5, 82.9, 71.9, 71.1, 70.8, 64.9, 63.7, 57.6, 39.2, 26.4, 26.3, 25.2 (3Me), 25.1, 23.3, 23.2, 22.9 (3Me), 14.4.

(2*S*,5*R*,1′*R*)-21 and (2*S*,5*R*,1′*S*)-22. The dioxolanone (2*S*,5*S*)-**2** (0.330 g, 1.31 mmol) was reacted with imine (*S*)-**11** (0.120 g, 035 mmol). Silica gel column chromatography of the crude compound (*n*-hexane/EtOAc, 11:9) afforded (2*S*,5*R*,1′*R*)-**21** and (2*S*,5*R*,1′*S*)-**22** as a 1:1 mixture (0.12 g, 0.20 mmol, 58%). IR (Nujol, cm^{-1}): 2984, 1785, 1375, 1254, 1077. MS (*m*/*z*): 582 $(M^+ + 1)^+$, 477, 462, 219. HRMS *m*/*z* calcd for $C_{29}H_{43}NO_9S$ $[M]^+$, 581.2658; *m*/*z* found, 581.2647. ^{1}H NMR ($CDCl_3$): δ 7.75−7.70 (m, 2H, arom), 7.40−7.25 (m, 3H, arom), 5.70 (s, 0.5H), 5.56 (s, 0.5H), 5.49 (d, 0.5H, J = 5.2 Hz), 5.36−5.32 (m, 1H), 4.65 (d, 0.5H, J = 8.4 Hz), 4.44−4.36 (d, 1.5H), 4.34−4.30 (m, 1H), 4.22−4.18 (m, 0.5H), 4.08 (m, 0.5H, J = 5.2 Hz), 3.85 (d, 0.5H, J = 8.4 Hz), 3.69 (d, 0.5H, J = 8.4 Hz), 3.47 (d, 0.5H, J = 4.0 Hz), 1.48 (s, 1.5H, Me), 1.45 (s, 1.5H, Me), 1.33 (s, 1.5H, Me), 1.27 (s, 4.5H, 3Me), 1.23 (s, 4.5H, 3Me), 1.22−1.20 (b, 3H, 2Me), 1.13 (s, 3.0H, 2Me), 0.98 (s, 4.5H, 3Me), 0.91 (s, 4.5H, 3Me), 0.7 (s, 1.5H, Me). ^{13}C NMR ($CDCl_3$): δ 172.4, 170.8, 136.0, 135.4 129.0, 128.8, 128.6, 128.5, 126.5, 125.0, 111.3, 109.8, 109.1, 109.0, 108.9, 108.4, 96.7, 96.2, 85.4, 82.8, 72.1, 72.0, 71.0, 70.9, 70.8, 70.6, 66.5, 65.4, 63.5, 57.7, 56.6, 55.4, 35.2, 35.1, 26.3, 26.3, 25.4, 25.4, 25.1, 25.0, 24.8, 23.9, 23.7, 23.2, 23.1, 22.7. Anal. Calcd for $C_{29}H_{43}NO_9S$: C, 59.88; H, 7.45; N, 2.41. Found: C, 59.72; H, 7.37; N, 2.33.

(2*S*,5*R*,1′*R*)-23. In a two-necked 50 mL round-bottom flask equipped with a nitrogen inlet, an injection septum, and a magnetic stirring bar were placed dioxolanone (2*S*,5*S*)-**1** (0.26 g, 1.52 mmol) and 15 mL of freshly distilled THF. The reaction mixture was cooled to −78 °C, and a solution of 1 M LHMDS (1.6 mL, 1.53 mmol) was added dropwise. The solution was stirred for 45 min at −60 °C then cooled to −80 °C. HMPA (1.6 mL) was added dropwise, and after an additional 5 min a solution of (5-*tert*-butylsulfinyliminomethyl)-2′,3′-di-*tert*-butyldimethylsilyl-uridine (*S*)-**12** (0,22 g, 0.38 mmol) in dry THF (6.08 mL) was slowly added. The reaction mixture was stirred at −78 °C for a further 45 min, then quenched following the reported standard workup. Silica gel column chromatography of the crude compound (*n*-Hexane/EtOAc, 7:3) afforded (2*S*,5*R*,1′*R*)-**23** (0.25 g, 0.33 mmol, 87%): $[\alpha]^{20}_D$ +98.2 (c 4.0, $CHCl_3$). IR (Nujol, cm^{-1}): 2950, 1796, 1698, 1375, 1254, 1153, 1060. MS (*m*/*z*): 745 $(M)^+$, 640, 630, 516. HRMS *m*/*z* calcd for $C_{34}H_{63}N_3O_9SSi_2$ $[M]^+$, 745.3824; *m*/*z* found, 745.3832. ^{1}H NMR ($CDCl_3$): δ 8.4 (b, 1H, N*H*-CO), 7.44 (d, 1H, J = 8.0 Hz, H6′), 5.77 (d, 1H, J_1=8.0 Hz, H7′), 5.60 (d, 1H, J = 4.4 Hz, H5′) 4.90 (d, 1H, J = 9.6 Hz, H2′), 4.54 (dd, 1H, J_1=5.2 Hz, J_2=9.6 Hz, H3′), 4.53 (s, 1H, *H*N−SO), 4.43 (t, 1H, J = 4.5 Hz, H4′), 3.59 (d, 1H, J = 9.6 Hz, H1′), 1.51 (s, 3H, C2-Me), 1.42 (s, 3H, C5-Me), 1.30 (s, 9H, 3 Me), 0.97 (s, 9H, 3Me), 0.88 (s, 9H, 3Me), 0.86 (s, 9H, 3Me), 0.15 (s, 3H, Me), 0.11 (s, 3H, Me), 0.10 (s, 3H, Me), 0.03 (s, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 172.6, 162.3, 149.7, 143.5, 113.9, 103.1, 94.0, 81.8, 79.9, 72.6, 72.5, 61.1, 57.5, 38.9, 25.9, 25.8, 24.6, 23.7, 23.3, 18.9, 17.9, 17.8, −4.2, −4.3, −4.4, −4.8. Anal. Calcd for $C_{34}H_{63}N_3O_9SSi_2$: C, 54.73; H, 8.51; N, 5.63. Found: C, 54.53; H, 8.58; N, 5.70.

(2*S*,5*R*,1′*S*)-24. In a two-necked 50 mL round-bottom flask equipped with a nitrogen inlet, an injection septum, and a magnetic stirring bar were placed (0.33 g, 1.52 mmol) dioxolanone (2*S*,5*S*)-**2** and 23 mL of freshly distilled THF. The reaction mixture was cooled to −78 °C and a solution of 1 M LHMDS (2.5 mL, 2.4 mmol) was added dropwise. The solution was stirred for 45 min at −60 °C, then cooled to −80 °C. HMPA (2.3 mL) was added dropwise, and after an additional 5 min a solution of (5-*tert*-butylsulfinyliminomethyl)-2′,3′-di-*tert*-butyldimethylsilyl-uridine (*S*)-**12** (0.51 g, 2.29 mmol) in dry THF was slowly added. The reaction mixture was stirred at −78 °C for a further 45 min, then quenched following the reported standard workup. Silica gel column chromatography of the crude material (*n*-hexane/EtOAc, 7:3) afforded (2*S*,5*R*,1′*R*)-**23** (1.57 g, 2.01 mmol, 88%): HRMS *m*/*z* calcd for $C_{37}H_{61}N_3O_9SSi_2$ $[M]^+$, 779.3667; *m*/*z* found, 779.3674. ^{1}H NMR ($CDCl_3$): δ 9.4 (b, 1H, N*H*-CO), 7.63 (d, 1H, J = 8.0 Hz, H6′), 7.65−7.60 (m, 2H, arom), 7.35−7.29 (m, 2H, arom), 7.23−7.28 (m, 1H, arom), 5.82 (d, 1H, J = 3.5 Hz, H5′), 5.72 (dd, 1H, J_1=8.0 Hz, H7′), 5.43 (s, 1H, O−C*H*-O), 4.49 (t, 1H, J = 5.5 Hz, H3′), 4.44 (d, 1H, J = 10.0 Hz, NH), 4.25 (dd, 1H, J_1=3.5 Hz, J_2=5.5 Hz, H4′), 4.17 (d, 1H, J = 5.5 Hz, H2′), 3.97 (d, 1H, J = 10.0 Hz, H1′), 0.95 (s, 9H, 3Me), 0.93 (s, 9H, 3Me), 0.92 (s, 9H, 3Me), 0.88 (s, 9H, 3Me), 0.23 (s, 3H, Me), 0.11 (s, 3H, Me), 0.07 (s, 3H, Me), 0.03 (s, 3H, Me). ^{1}H NMR (C_6D_6): δ 8.6 (b, 1H, N*H*-CO), 7.93 (d, 2H, J = 7.5 Hz, arom), 7.1−7.00 (m, 2H, arom), 6.98 (t, 1H, J = 7.5 Hz, arom), 6.77 (d, 1H, J = 8.0 Hz, H6′), 5.66 (s, 1H, O−C*H*-O), 5.54 (d, 1H, J = 5.5 Hz, H5′), 5.48 (d, 1H, J = 10.0 Hz, NH), 5.33 (d, 1H, J_1=8.0 Hz, H7′), 4.86 (dd, 1H, J_1=4.0 Hz, J_2=5.5 Hz, H3′), 4.77 (t, 1H, J = 5.5 Hz, H4′), 4.64 (d, 1H, J = 4.0 Hz, H2′), 4.30 (d, 1H, J = 10.0 Hz, H1′), 1.05 (s, 9H, 3Me of OSi^{t}Bu), 0.94 (s, 9H, 3Me of O=S^{t}Bu), 0.92 (s, 9H, 3Me of OSi^t-Bu), 0.77 (s, 9H, 3Me of CH^{t}Bu), 0.36 (s, 3H, Me), 0.21 (s, 3H, Me), 0.20 (s, 3H, Me), 0.08 (s, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 171.4, 162.9, 150.0, 143.1, 136.3, 128.5, 128.4, 125.9, 109.9, 103.4, 93.0, 85.0, 82.1, 73.4, 72.2, 63.3, 57.1, 35.5, 26.1, 26.0, 23.8, 22.9, 18.1, 14.4, −4.2, −4.3, −4.5, −4.8. ^{13}C NMR (C_6D_6): δ 171.4, 162.2, 149.9, 143.7, 137.6, 128.3−127.6, 126.3, 109.7, 102.5, 95.0, 85.0, 84.7, 73.5, 72.0, 65.2, 56.7, 35.2, 26.01, 25.9, 23.4, 22.9, 18.1, 18.0, −4.0, −4.1, −4.3, −4.9. Anal. Calcd for $C_{37}H_{61}N_3O_9SSi_2$: C, 56.96; H, 7.88; N, 5.39. Found: C, 56.70; H, 7.93; N, 5.35.

General Procedure for Synthesis of Methyl *β*-Sulfinylaminopropionates. To a solution of 1′-sulfinylaminodioxolanone in dry methanol (3.0 mL × 0.1 g) were added 1.5 equiv of a freshly prepared 1.5 M solution of MeONa in MeOH. The solution was stirred under nitrogen at 65 °C until no starting 1′-sulfinylaminodioxolanone was detected by TLC analysis. After cooling, the reaction 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, filtered, and concentrated under vacuum. Silica gel column chromatography (EtOAc/*n*-hexane, 1:2) of the crude compound afforded the corresponding aminoesters.

(2*R*,3*R*)-25. The reaction of (2*S*,5*R*,1′*R*)-**13** (0.12 g, 0.14 mmol) with 0.17 mmol of MeONa afforded (2*R*,3*R*)-**25** (0.10 g, 0.128 mmol, 92%): $[\alpha]^{20}_D$ +28.9 (c 0.8, $CHCl_3$). IR (Nujol, cm^{-1}): 2932, 1707, 1455, 1260, 1082. MS *m*/*z* 760 $(M)^+$, 746, 653, 524, 417. HRMS *m*/*z* calcd for $C_{43}H_{54}NO_9S$ $[M+1]^+$, 760.3519; *m*/*z* found, 760.3531. ^{1}H NMR ($CDCl_3$): δ 7.40−7.15 (m, 20H, arom), 5.05 (d, 1H, J = 2.0 Hz), 4.89 (d, 1H, J = 12.0 Hz), 4.85 (d, 1H, J = 11.0 Hz), 4.76 (d, 1H, J = 11.0 Hz), 4.75 (d, 1H, J = 1.0 Hz), 4.54 (d, 1H, J = 11.0 Hz), 4.54 (d, 1H, J = 12.0 Hz), 4.49 (d, 1H, J = 12.0 Hz), 4.16−4.10 (m, 1H), 3.88−3.82 (m, 2H), 3.80−3.68 (m, 3H), 3.64 (s, 3H, Me), 3.64−3.60 (m, 1H), 3.56−3.44 (m, 3H), 1.84−1.60 (b, 2H, NH_2), 1.45 (s, 3H, Me), 1.39 (s, 3H, Me), 1.16 (s, 9H, 3Me). ^{13}C NMR ($CDCl_3$): δ 175.8, 138.8, 138.5, 138.2, 138.1, 128.6−127.4, 87.3, 81.3, 79.1, 78.7, 78.2, 77.0, 75.3, 75.0, 73.6, 73.4, 69.3, 63.2, 56.9, 52.6, 24.4, 23.0. Anal. Calcd for $C_{43}H_{53}NO_9S$: C, 67.96; H, 7.03; N, 1.84. Found: C, 67.84; H, 7.11; N, 1.96.

General Procedure of Selective *N*-Sulfinyl Deprotection. Unless otherwise stated, a MeOH solution of the *N*-sulfinylaminodioxolanone (2 mL × 0.03 g of dioxolanone) was added to a solution (Et_2O) of 2 N HCl (16 equiv) under argon at 0 °C. After 30 min, the temperature was raised to 25 °C, and the mixture was stirred for 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 concentrated under vacuum. The residue was purified by flash silica gel column chromatography (cyclohexane/EtOAc/*i*PrNH_2, 15:4.9:0.1).

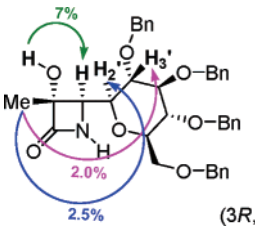
(2*S*,5*R*,1′*R*)-33. The reaction of (2*S*,5*R*,1′*R*)-**13** (0.11 g, 0.13) with 1.0 mL of 2.0 N HCl afforded (2*S*,5*R*,1′*R*)-**33** (0.09 g, 0.12

mmol, 94%): $[\alpha]^{20}_D$ +17.8 (c 0.8, $CHCl_3$). IR (Nujol, cm^{-1}): 1780, 1453, 1068. MS *m/z* 724 $(M+1)^+$, 666, 552, 444, 353, 181. HRMS *m/z* calcd for $C_{44}H_{53}NO_8Na$ $[M + Na]^+$, 746.3669; *m/z* found, 746.3651. ^1H NMR ($CDCl_3$): δ 7.40−7.10 (m, 20H, arom), 5.11 (d, 1H, J = 11.5 Hz), 4.96 (d, 1H, J = 11.0 Hz), 4.82 (s, 1H), 4.80 (s, 1H), 4.74 (d, 1H, J = 11.5 Hz), 4.62 (d, 1H, J = 11.0 Hz), 4.60 (d, 1H, J = 12.4 Hz), 4.50 (d, 1H, J = 12.0 Hz), 3.84−3.62 (m, 5H), 3.56 (dd, 1H, J_1=4.4 Hz, J_2=8.8 Hz), 3.44−3.38 (m, 1H), 3.35 (d, 1H, J = 5.2 Hz), 1.8−2.0 (b, 2H, NH_2), 1.45 (s, 3H, Me), 1.37 (s, 3H, Me), 0.96 (s, 9H, 3 Me). ^{13}C NMR ($CDCl_3$): δ 175.4, 138.6, 138.5, 138.4, 138.3, 138.2, 128.7−127.3, 115.0, 88.2, 81.2, 79.5, 79.2, 79.0, 78.5, 75.6, 75.1, 73.9, 73.7, 69.1, 60.0, 39.1, 25.1, 22.8, 20.6. Anal. Calcd for $C_{44}H_{53}NO_8$: C, 73.00; H, 7.38; N, 1.92. Found: C, 72.84; H, 7.41; N, 1.85.

General Procedure of Synthesis of *β*-Lactams. The *β*-lactams were prepared according to a modified literature protocol. In a two-necked 50 mL round-bottom flask equipped with a nitrogen inlet, an injection septum, and a magnetic stirring bar were placed the free aminodioxolanone and freshly distilled THF (1.0 mL × 0.03 g of dioxolanone). The reaction mixture was cooled to −30 °C, and a solution of LHMDS (1 M in THF, 4 equiv) and HMPA (0.1 mL × 0.030 g of dioxolanone) was added dropwise. The reacion mixture was warmed to −5 °C during 3 h and then quenched with 1.0 N HCl. The *β*-lactams were isolated according to the following standard procedure: The reaction mixture was extracted with ethyl acetate (3 × 20 mL), and the collected organic phases were washed with saturated NH_4Cl, then dried over Na_2SO_4. After filtration, the solvent was removed under vacuum, and the residue was purified by flash column chromatography to afford the desired *β*-lactam.

(3*R*,4*R*)-41. An amount of 0.49 mL of 1.0 M solution of LHMDS in THF and 0.30 mL of HMPA were added to a solution of (2*S*,5*R*,1′*R*)-**33** (0.091 g, 0.12 mmol). The reaction was quenched after 85% conversion of the starting material **33**. Purification by flash column chromatography afforded (3*R*,4*R*)-**41** (0.06 g; 0.096 mmol; 80%): $[\alpha]^{20}_D$ +32.9 (c 0.6, $CHCl_3$). IR (Nujol, cm^{-1}): 3412, 2906, 1770, 1453, 1361. MS *m/z* 551 $(M-HOMeC{=}CO)^+$, 532, 504, 91. HRMS *m/z* calcd for $C_{38}H_{41}NO_7$ $[M]^+$, 623.2883; *m/z* found, 623.2880. ^1H NMR (CD_3COCD_3): δ 7.40−7.10 (m, 20H, arom), 6.50 (s, 1H, NH), 5.11 (b, 1H, OH), 4.96 (d, 1H, J = 11.0 Hz), 4.95 (d, 1H, J = 11.5 Hz), 4.90 (d, 1H, J = 11.0 Hz), 4.85 (d, 1H, J = 11.5 Hz), 4.81 (d, 1H, J = 11.5 Hz), 4.67 (d, 1H, J = 11.5 Hz), 4.58 (d, 1H, J = 12.0 Hz), 4.56 (d, 1H, J = 12.0 Hz), 3.78 (dd, 1H of CH_2, J_1=2.0 Hz, J_2=11.0 Hz), 3.77 (t, 1H, J = 9.0 Hz, H4′), 3.71 (dd, 1H of CH_2, J_1=4.0 Hz, J_2=11.0 Hz), 3.64 (d, 1H, J = 7.5 Hz, H4), 3.63 (t, 1H, J = 9.0, H5′), 3.57 (t, 1H, J = 9.2, H3′), 3.53 (ddd, J_1=2.0 Hz, J_2=4.0 Hz, J_3=9.0 Hz, H6′), 3.48 (dd, 1H, J_1=7.5 Hz, J_2=9.0 Hz, H2′), 1.53 (s, 3H, Me). ^{13}C NMR (CD_3COCD_3): δ 171.2, 139.2, 139.0, 138.9, 138.7, 128.6−127.5, 87.2, 85.9, 81.5, 79.2, 79.0, 77.8, 75.2, 74.7, 74.4, 73.0, 69.3, 63.1, 17.5. Anal. Calcd for $C_{38}H_{41}NO_7$: C, 73.17; H, 6.63; N, 2.25. Found: C, 72.94; H, 6.55; N, 2.35.

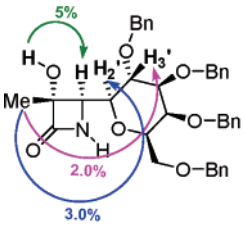
Homonuclear NOE Experiments (CD_3COCD_3). Irradiation of the O**H** (5.11 ppm) showed a 7% NOE on the C4-**H** at 3.63 ppm. No NOE effect was observed on C4-H upon irradiation of the C3-**Me** at 1.53 ppm. However, irradiation of the C3-Me caused an enhancement of 2.5% and 2% with the C-H's of the glucopyranosyl moiety centered at 3.48 ppm (H2′) and 3.57 ppm (H3′), respectively. These results allowed the assignment of the (3*R*,4*R*) configuration to the reported *β*-lactam.



(3*R*, 4*R*)-**41**

(3*R*,4*R*)-42. An amount of 0.57 mL of 1.0 M solution of LHMDS in THF and 0.40 mL of HMPA were added to a solution of (2*S*,5*R*,1′*R*)-**35** (0.11 g, 0.14 mmol). The reaction was quenched after 90% conversion of the starting material **35**. Purification by flash column chromatography afforded (3*R*,4*R*)-**42** (0.073 g; 0.12 mmol; 86%): $[\alpha]^{20}_D$ +23.4 (c 0.4, $CHCl_3$). IR (Nujol, cm^{-1}): 3406, 2925, 1764, 1450. MS *m/z* 622 $(M - 1)^+$, 552, 504, 444, 354, 181. HRMS *m/z* calcd for $C_{38}H_{41}NO_7$ $[M]^+$, 623.2883; *m/z* found, 623.2891. ^1H NMR (CD_3COCD_3): δ 7.40−7.10 (m, 20H, arom), 6.48 (s, 1H, NH), 4.99 (d, 1H, J = 10.5 Hz), 4.98 (b, 1H, OH), 4.97 (d, 1H, J = 10.5 Hz), 4.91 (d, 1H, J = 11.5 Hz), 4.79 (d, 1H, J = 10.5 Hz), 4.75 (d, 1H, J = 11.5 Hz), 4.63 (d, 1H, J = 11.5 Hz), 4.56 (d, 1H, J = 12.4 Hz), 4.51 (d, 1H, J = 12.4 Hz), 4.19 (dd, 1H, J_1=1.2 Hz, J_2=3.0 Hz, H5′), 3.93 (t, 1H, J = 9.2 Hz, H3′), 3.83 (dd, 1H, J_1=3.0 Hz, J_2=9.2 Hz, H4′), 3.73 (dt, 1H, J_1=1.2 Hz, J_2=6.5 Hz, J_3=7.0 Hz, H6′), 3.68−3.58 (m, 2H, CH_2), 3.60 (d, 1H, J = 7.0 Hz, H4), 3.41 (dd, 1H, J_1=7.0 Hz, J_2=9.2 Hz, H2′), 1.47 (s, 3H, Me). Anal. Calcd for $C_{38}H_{41}NO_7$: C, 73.17; H, 6.63; N, 2.25. Found: C, 73.13; H, 6.52; N, 2.19.

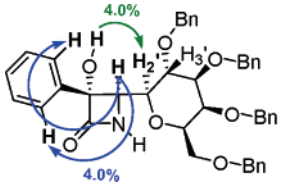
Homonuclear NOE Experiments (CD_3COCD_3). Irradiation of O**H** (4.98 ppm) showed a 5% NOE on the C4-H at 3.60 ppm. No NOE was observed on C4-H upon irradiation of the C3-Me (1.47 ppm). However, irradiation of the C3-Me caused an enhancement of 3.0% and 2% with the C-H's of the galactopyranosyl moiety centered at 3.41 ppm (H2′) and 3.93 ppm (H3′), respectively. These results allowed the assignment of the (3*R*,4*R*) configuration to the reported *β*-lactam.



(3*R*, 4*R*)-**42**

(3*R*,4*S*)-43. An amount of 0.66 mL of 1.0 M solution of LHMDS in THF and 0.45 mL of HMPA were added to a solution of (2*S*,5*R*,1′*S*)-**36** (0.13 g, 0.17 mmol). Purification of the crude compound afforded (3*R*,4*S*)-**43** (0.04 g, 0.06 mmol, 35%): $[\alpha]^{20}_D$ −54.5 (c 0.3, $CHCl_3$). IR (Nujol, cm^{-1}): 3418, 2913, 1773. MS *m/z* 686 $(M)^+$, 552, 525, 502. HRMS *m/z* calcd for $C_{43}H_{43}NO_7$ $[M]^+$, 685.3040; *m/z* found, 685.3028. ^1H NMR (CD_3COCD_3): δ 7.73 (s, 1H, NH), 7.51 (m, 2H arom), 7.50 (m, 2H, arom), 7.40−7.20 (m, 16H, arom), 5.14 (s, 1H, OH), 4.97 (d, 1H, J = 11.5 Hz), 4.93 (d, 1H, J = 11.5 Hz), 4.91 (d, 1H, J = 12.0 Hz,), 4.77 (d, 1H, J = 12.0 Hz), 4.62 (d, 2H, J = 11.5 Hz), 4.56 (s, 2H), 4.21 (dd, 1H, J_1=0.8 Hz, J_2=2.4 Hz, H5′), 3.98 (d, 1H, J = 2.4 Hz, H4), 3.97−3.90 (m, 3H, H4′, H6′, and 1H of CH_2), 3.75 (dd, 1H of CH_2, J_1=8.4 Hz, J_2=9.6 Hz), 3. 70 (dd, 1H, J_1=2.4 Hz, J_2=9.2 Hz, H2′), 3. 55 (dd, 1H, J_1=4.0 Hz, J_2=9.6 Hz, H3′). ^{13}C NMR (CD_3COCD_3): δ 170.4, 139.6, 139.3, 139.0, 138.7, 138.6, 128.6−127.5, 88.5, 84.7, 77.9, 76.8, 75.8, 75.1, 74.9, 74.6, 73.1, 72.1, 69.6, 61.5. Anal. Calcd for $C_{43}H_{43}NO_7$: C, 75.31; H, 6.32; N, 2.04. Found: C, 75.10; H, 6.45; N, 1.96.

Homonuclear NOE Experiments (CD_3COCD_3). Irradiation of the O**H** (5.14 ppm) showed a 4% NOE on the H2′ of the galactopyranosyl moiety centered at 3.70 ppm. No NOE was observed on C4-H at 3.98 ppm upon irradiation of the O**H**. The irradiation of C4-H showed a 4% NOE on the ortho aromatic

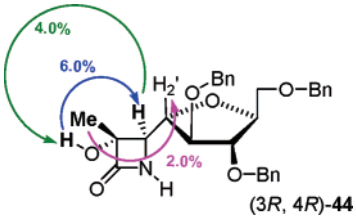


(3*R*, 4*S*)-**43**

protons (7.51 ppm) of the C_6H_5 substituent at the β-lactam.. These results allowed the assignment of the (3R,4S) configuration to the reported β-lactam.

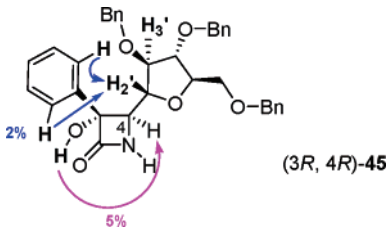
(3*R*,4*R*)-44. An amount of 0.63 mL of 1.0 M solution of LHMDS in THF and 0.30 mL of HMPA were added to a solution of (2*S*,5*R*,1′*R*)-**37** (0.095 g, 0.16 mmol). The reaction was quenched after 87% conversion of the starting material **37**. Purification by flash column chromatography afforded (3*R*,4*R*)-**44** (0.06 g; 0.12 mmol; 76%): $[\alpha]^{20}_D$ +52.1 (c 0.6, $CHCl_3$). IR (Nujol, cm^{-1}): 3352, 1751, 1090. MS *m*/*z* 503 $(M)^+$, 431, 323, 181. HRMS *m*/*z* calcd for $C_{30}H_{33}NO_6$ $[M]^+$, 503.2308; *m*/*z* found, 503.2314. ^{1}H NMR (CD_3COCD_3): δ 7.40−7.30 (m, 15H, arom), 7.23 (s, 1H, NH), 5.07 (s, 1H, OH), 4.65−4.55 (m, 6H, $3CH_2$), 4.26 (ddd, 1H, J_1=6.4 Hz, J_2=8.8 Hz, J_3=1.6 Hz, H5′), 4.22−4.18 (t, 1H, J = 1.6 Hz, H4′), 4.13 (dd, 1H, J_1=3.2 Hz, J_2=7.2 Hz, H2′), 4.07 (dd, 1H J_1=1.6 Hz, J_2=3.2 Hz, H3′), 3.70 (d, 1H, J = 7.2 Hz, H4), 3.62−3.58 (m, 2H, CH_2), 1.37 (s, 3H, Me). ^{13}C NMR (CD_3COCD_3): δ 171.0, 138.9, 138.4, 138.3, 128.5−127.6, 86.0, 84.5, 84.2, 83.3, 83.1, 73.0, 71.7, 71.5, 70.5, 63.3, 17.5. Anal. Calcd for $C_{30}H_{33}NO_6$: C, 71.55; H, 6.61; N, 2.78. Found: C, 71.81; H, 6.60; N, 2.86.

Homonuclear NOE Experiments (CD_3COCD_3). Irradiation of the O**H** (5.07 ppm) showed a 6% NOE on the C4-H at 3.70 ppm, and the irradiation of the C4-**H** (3.70 ppm) produced a 4% NOE on the C3-O**H**. No NOE was observed on C4-H upon irradiation of the C3-**Me** at 1.37 ppm, but this caused an enhancement of 2.0% to the signal of the sugar moiety centered at 4.13 ppm (H2′). These results allowed an assignment of the (3R,4R) configuration to the reported β-lactam.



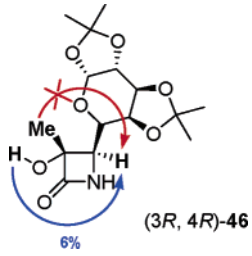
(3*R*,4*R*)-45. An amount of 0.69 mL of 1.0 M solution of LHMDS in THF and 0.30 mL of HMPA were added to a solution of (2*S*,5*R*,1′*R*)-**38** (0.11 g, 0.17 mmol). The reaction was quenched after 90% conversion of the starting material **38**. Purification by flash column chromatography afforded (3*R*,4*R*)-**45** (0.07 g; 0.13 mmol; 77%): $[\alpha]^{20}_D$ +9.8 (c 0.4, $CHCl_3$). IR (Nujol, cm^{-1}): 1753, 1495, 1453. MS (*m*/*z*): 458 $(M^+ - OCH_2C_6H_5)^+$, 431, 368, 325, 181, 106, 91. HRMS *m*/*z* calcd for $C_{35}H_{35}NO_6$ $[M]^+$, 565.2464; *m*/*z* found, 565.2450. ^{1}H NMR (CD_3COCD_3): δ 7.82 (s, 1H, NH), 7.60−7.56 (m, 2H, arom), 7.45−7.20 (m, 16H, arom), 7.02−6.96 (m, 2H, arom), 5.86 (s, 1H, OH), 4.65 (d, 1H, J = 12.0 Hz), 4.60 (d, 1H, J = 12.0 Hz), 4.49 (d, 1H, J = 12.0 Hz), 4.44 (d, 1H, J = 12.0 Hz), 4.22 (ddd, 1H, J_1=6.0 Hz, J_2=6.8 Hz, J_3=2.0 Hz, H5′), 4.08 (d, 1H, J = 10.5 Hz, H4), 4.00 (d, 1H, J = 2.0 Hz, H4′), 3.85 (d, 1H of CH_2, J = 11.5 Hz), 3.80 (s, 1H, H3′), 3.73 (d, 1H, J = 10.5 Hz, H2′), 3.64 (d, 1H of CH_2, J = 11.5 Hz), 3.46 (dd, 1H of CH_2, J_1=6.0 Hz, J_2=9.5 Hz), 3.41 (dd, 1H of CH_2, J_1=6.8 Hz, J_2=9.5 Hz). ^{13}C NMR (CD_3COCD_3): δ 169.3, 138.9, 138.4, 138.3, 137.5, 128.5−127.2, 85.2, 84.7, 84.4, 83.5, 73.0, 71.6, 71.2, 70.8, 70.6, 63.0. Anal. Calcd for $C_{35}H_{35}NO_6$: C, 74.32; H, 6.24; N, 2.48. Found: C, 74.51; H, 6.30; N, 2.56.

Homonuclear NOE Experiments (CD_3COCD_3). Irradiation of the O**H** (5.86 ppm) showed a 5% NOE on the C4-**H** of the β-lactam ring (3.73 ppm). Irradiation of the ortho aromatic protons of the C_6H_5 substituent in the region between 7.6 and 7.56 ppm, caused an enhancement of 2.0% on the **H2′** signal of the sugar ring. Accordingly, the irradiation of H2′ produced a 3.0% NOE on the ortho aromatic protons of the benzene ring. These results allowed to assign the (3R,4R) configuration to the reported β-lactam.



(3*R*,4*R*)-46. An amount of 0.86 mL of 1.0 M solution of LHMDS in THF and 0.30 mL of HMPA were added to a solution of (2*S*,5*R*,1′*R*)-**39** (0.09 g, 0.21 mmol). The reaction was quenched after 90% conversion of the starting material **39**. Purification by flash column chromatography afforded (3*R*,4*R*)-**46** (0.05 g, 0.16 mmol, 76%): $[\alpha]^{20}_D$ −14.5 (c 0.50, $CHCl_3$). IR (Nujol, cm^{-1}): 1766, 1488, 1444. MS (*m*/*z*): 329 $(M)^+$, 316, 258, 230. HRMS *m*/*z* calcd for $C_{15}H_{23}NO_7$ $[M]^+$, 329.1475; *m*/*z* found, 329.1482. ^{1}H NMR (CD_3COCD_3): δ 6.81 (s, 1H, NH), 5.51 (d, 1H, J = 5.2 Hz, H6′), 4.97 (s, 1H, OH), 4.65 (dd, 1H, J_1=2.5 Hz, J_2=8.0 Hz, H4′), 4.38−4.34 (m, 2H, H5′ and H3′), 3.91 (dd, 1H, J_1=1.6 Hz, J_2=4.8 Hz, H2′), 3.68 (d, 1H, J = 4.8 Hz, H4), 1.50 (s, 3H, Me), 1.41 (s, 6H, 2Me), 1.33 (s, 6H, 2Me). ^{13}C NMR (CD_3COCD_3): δ 171.0, 109.2, 108.5, 96.7, 84.7, 73.2, 71.0, 70.6, 65.6, 25.6, 24.5, 23.8, 17.4. Anal. Calcd for $C_{15}H_{23}NO_7$: C, 54.70; H, 7.04; N, 4.25. Found: C, 54.55; H, 7.11; N, 4.15.

Homonuclear NOE experiments (CD_3COCD_3). Irradiation of the O**H** (4.97 ppm) showed a 6% NOE on the C4-**H** at 3.68 ppm of the β-lactam ring. No NOE on C4-H was observed upon irradiation of the C3-**Me** (1.50 ppm); therefore, the stereochemistry of the β-lactam is (3*R*,4*R*).



Supporting Information Available: Spectroscopic and analytical data for compounds **7**, **26**−**32**, **34**−**40**, and 3,4-bis-(*tert*-butyldimethyl-silanyloxy)-5-hydroxymethyl-tetrahydro furan-2-yl]-1H-pyrimidine-2,4-dione, including ^{1}H and ^{13}C NMR spectra of compounds **8**−**46**, and X-ray crystallographic data for compounds **23** and **26** as a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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