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1′-Azido- and 1′-amino-1,3-dioxolan-4-ones

Arturo Battaglia,* Gaetano Barbaro, Patrizia Giorgianni, Andrea Guerrini and Antonella Pepe

Istituto CNR dei Composti del Carbonio Contenenti Eteroatomi 'I.Co.C.E.A.', via Gobetti 101, I-40129 Bologna, Italy

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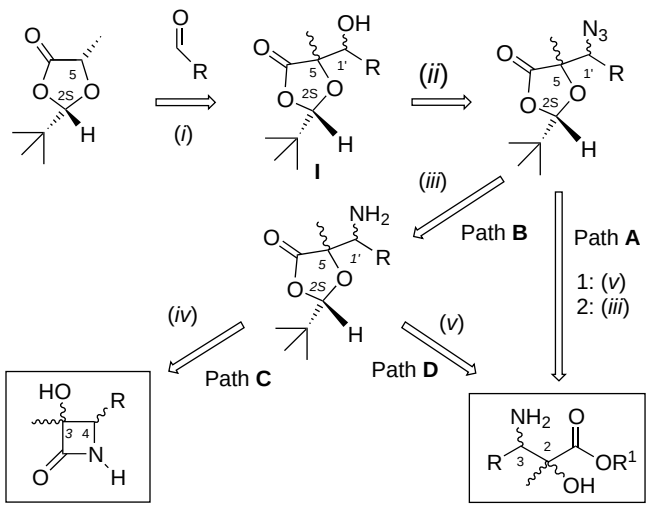
Abstract—1,3-Dioxolanone alcohols, prepared via the addition of chiral lithium enolates of 1,3-dioxolan-4-ones to aldehydes, are suitable intermediates for the synthesis of chiral trisubstituted isoserines or trisubstituted 3-hydroxy-β-lactams. In particular, the methyl ester of 2-methyl-3-(2-furyl)isoserinic acid and two 3-methyl-3-hydroxy-β-lactams bearing either a 2-furyl or a phenyl substituent at C-(4) have been prepared. The (2*R*,3*S*) stereochemistry of the isoserine, and the (3*R*,4*S*) stereochemistry of the two β-lactams is that required for the synthesis of taxoid analogues having the side-chain with the proper (2′*R*,3′*S*) configuration.

1. Introduction

Recently, we have developed a protocol for the synthesis of (4*S*)/(4*R*) diastereomeric mixtures of (3*R*)-3-hydroxy-β-lactams with a quaternary stereogenic center at C-(3) by addition of imines to (2*S*)-lithium enolates of (2*S*,5*S*)-1,3-dioxolan-4-ones in a mixed THF:HMPA (4:1) solvent system.[1] From a practical point of view the (2*S*,5*S*)-1,3-dioxolan-4-one starting materials are easily prepared from inexpensive and readily available (2*S*)-hydroxy acids. A major pitfall of this protocol is that the low reactivity of the imines requires the use of a toxic HMPA co-solvent. Therefore, we considered replacing the imines with the more reactive aldehydes, which would represent a new approach to trisubstituted isoserines and 3-hydroxy-β-lactams. Seebach's diastereoselectivity studies[2] on the addition reactions of (2*S*)-enolates of dioxolanones to aldehydes, which gave dioxolanone alcohols **I**, seemed to us a good starting point to explore the new methodology according to the sequence of reactions depicted in Scheme 1. Access to isoserines and 3-hydroxy-β-lactams requires the development of new methodology for the stereoselective conversion of 1′-hydroxy dioxolanones into 1′-azido dioxolanones. These products can be directly transformed into isoserines by removal of the acetal center via base induced solvolysis followed by reduction of the azido group (path **A**). Alternatively, the C-(1′)-N_3 group can be transformed into an amino group affording 1′-amino dioxolanones (path **B**), from which, by use of suitable protocols, both isoserines and β-lactams can be synthesized. Surprisingly, no methods have been reported for the preparation of 1′-amino dioxolanones whose structure places them as leading candidates as building blocks for EPC syntheses of a special class of β-peptides bearing in their skeleton a quaternary stereogenic center as a bend promoter.[3] As the only exce-



(*i*) Aldol addition; (*ii*) azidation; (*iii*) reduction; (*iv*) cyclization; (*v*) alcoholysis

Scheme 1. Suggested protocol for the conversion of dioxolanone alcohols into trisubstituted isoserines and 3-hydroxy-β-lactams.

* Corresponding author. Fax: (+39)51-6398349; e-mail: battaglia@area.bo.cnr.it

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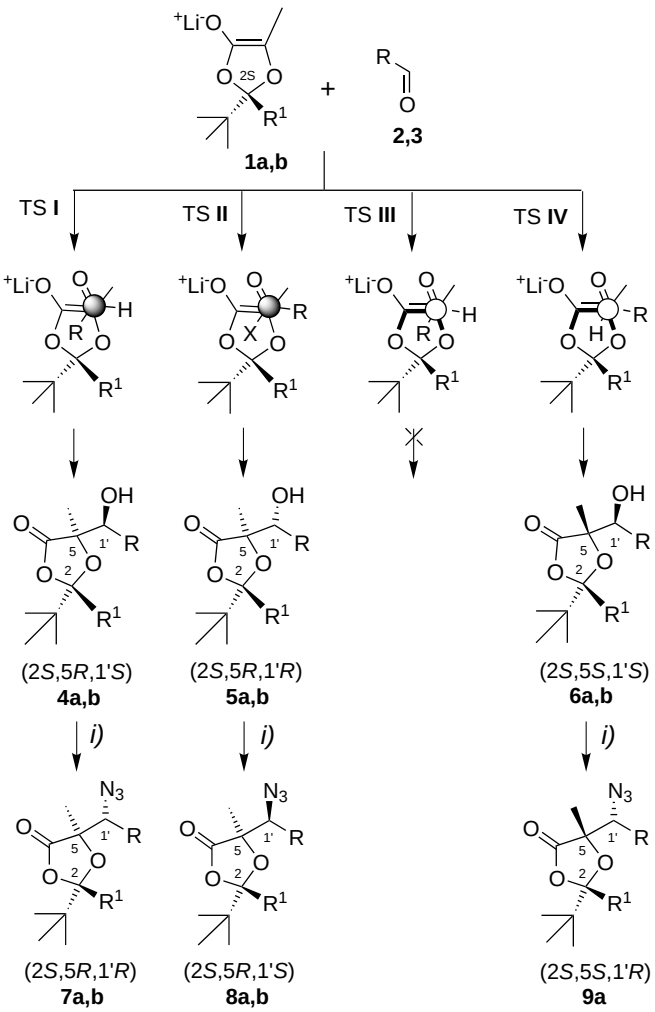
tion, we have recently described the synthesis of a 1′-amino dioxolan-4-one derived from the addition reaction of the enolates of **1a** to *N*-trimethylsilylphenyl aldimine under special reaction conditions.[1d] Another very important use of 1′-amino dioxolanones would be the synthesis of α,α-disubstituted 2′-hydroxy-β-amino acids (isoserines), intramolecularly protected both at the carbonyl and adjacent OH substituent. Consequently, the free 1′-amino group could be coupled with the carboxylic function of another amino acid. Alternatively, the 1′-amino dioxolanones can be transformed into β-lactams (path **C**) for peptide synthesis via Ojima's 'β-lactam synthon method'.[4] Very important targets from 1′-amino dioxolanones are also (3*R*,4*S*)-trisubstituted β-lactams and (2*R*,3*S*)-α,α-disubstituted isoserines with the correct stereochemistry to append to the 13-OH of taxoids.[5] Methodologies for the synthesis of these highly functionalized appendants are still scarce. Kant, Greene and Ojima independently developed approaches for the synthesis of suitable precursors of these appendants such as *N*,*O*-protected trisubstituted (2*R*,3*S*)-isoserines and (3*R*,4*S*)-β-lactams.[6] However, these intermediates were obtained in low yields via multi-step processes, which require the use of expensive chiral auxiliaries and several deprotection/reprotection sequences.

The key step in the protocol outlined in Scheme 1 is the azidation of the C-(1′) hydroxyl group and, herein, we describe our attempts to carry out its conversion to an azide moiety with inversion of configuration, and its subsequent reduction to an amine functionality.[7]

2. Results and discussion

The starting substrates tested for the development of our methodology were the dioxolanone alcohols obtained by the addition reactions of 2-furylaldehyde **3** to the lithium enolate **1a** (ratio of (2*S*):(2*R*) = 97:3) and benzaldehyde **2** to the lithium enolate **1b** (ratio of (2*S*):(2*R*) = 93:7),[8] respectively (Scheme 2). Synthesis of the dioxolanone alcohols lacked stereochemical control at C-(5) and C-(1′)[8] and mixtures of three isomers were obtained (Scheme 2 and Table 1). The (2*S*,5*R*,1′*S*) diastereoisomer formed via TS **I**, the (2*S*,5*R*,1′*R*) diastereoisomer via TS **II** and the (2*S*,5*S*,1′*S*) diastereoisomer, formed via TS **IV**. The aldol condensation of aldehyde **2** with enolate **1b** yielded a mixture of (2*S*,5*R*,1′*S*)-**4b**, (2*S*,5*R*,1′*R*)-**5b**, and (2*S*,5*S*,1′*S*)-**6b**, which were separated by flash chromatography.[8] The addition reaction of aldehyde **3** to the enolate **1a** yielded the dioxolanone alcohols (2*S*,5*R*,1′*S*)-**4a**, (2*S*,5*R*,1′*R*)-**5a**, and (2*S*,5*S*,1′*S*)-**6a**. Chromatography



1a: R^1 = H; **1b**: R^1 = Me; **2**: R = C_6H_5; **3**: R = 2-furyl; **4a**, **5a**, **6a**, **7a**, **8a**, **9a**: R = 2-furyl, R^1 = H; **4b**, **5b**, **6b**, **7b**, **8b**: R = C_6H_5, R^1 = Me; *i)* $ZnN_6.2Py/PPh_3/R^2CO_2$-N=N-CO_2R^2 (R^2: ^{i}Pr, ^{t}Bu)

Scheme 2. Synthesis of 1′-azido dioxolanones by azidation of dioxolanone alcohols.

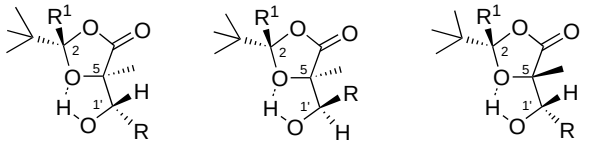
of the crude mixture gave (2*S*,5*S*,1′*S*)-**6a** and a mixture of (2*S*,5*R*,1′*R*)-**5a** and (2*S*,5*R*,1′*S*)-**4a**. Quantities of pure **5a** were isolated by fractional crystallization of this mixture. The diastereoisomer **4a** was isolated as the major of a 9:1 (2*S*,5*R*,1′*S*)/(2*S*,5*R*,1′*R*) diastereoisomeric mixture by recrystallization. Alternatively, an exploratory investigation showed that all the isomers could be efficiently separated by preparative HPLC.

The stereochemistry of **4b**, **5b**, and **6b** has been assigned previously.[8] In particular, the stereochemistry of

Table 1. Relative product distribution of dioxolanone alcohols[a,b]

Entry	Product	(2*S*,5*S*,1′*S*)	(2*S*,5*R*,1′*R*)	(2*S*,5*R*,1′*S*)	Total yield (%)
1	**a**	**4**: 19	**5**: 46	**6**: 35	80
2	**b**	**4**: 19	**5**: 63	**6**: 18	89

[a] THF at −78°C.
[b] Determined by ^{1}H NMR directly on the crude reaction mixture.



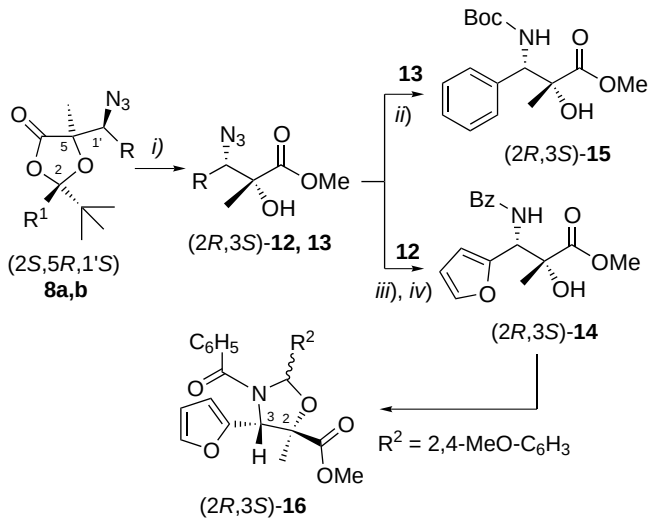
(2*S*,5*R*,1′*S*)-**4a,b** (2*S*,5*R*,1′*R*)-**5a,b** (2*S*,5*S*,1′*S*)-**6a,b**

a: R = 2-furyl, R^1 = H; **b**: R = C_6H_5, R^1 = Me

Figure 1. Five-membered ring chelate structures of dioxolanone alcohols (2*S*,5*R*,1′*S*)-**4a**,**b**, (2*S*,5*R*,1′*R*)-**5a**,**b**, and (2*S*,5*S*,1′*S*)-**6a**,**b**.

(2*S*,5*S*,1′*S*)-**6b** was established by X-ray structural analysis. The stereochemistry of (2*S*,5*R*,1′*R*)-**5b**, and (2*S*,5*R*,1′*S*)-**4b** were assigned by chemical correlation with the corresponding methyl (2*R*,3*R*)- and (2*R*,3*S*)-2,3-dihydroxy-2-methyl-3-phenylpropanoates. The ^{1}H and ^{13}C NMR spectral data are consistent with the assumption that the main conformers exists in an intramolecular hydrogen bonded form of a five-membered ring structure (Fig. 1) that have been suggested to rationalize the ^{1}H and ^{13}C NMR spectral data of alicyclic 2,3-dihydroxy-α-methylcarbonyl compounds.[9] The diastereoisomers **4a**, **5a**, and **6a** showed consistent trends for the C-(2)H and C-(5)Me ^{1}H NMR resonances with those observed for **4b**, **5b**, and **6b** and other dioxolanone alcohols.[8] In fact, a *trans* relationship between the 2-furyl substituent at C-(1′) and the C-(2) proton is seen for both the (2*S*,5*S*,1′*S*) and (2*S*,5*R*,1′*S*) isomers in the five-membered ring structures, whereas a *cis* relationship exists in the (2*S*,5*R*,1′*R*) isomer. Accordingly, the C-(2)H signal of the (2*S*,5*R*,1′*R*) isomer ($\delta = 4.84$ ppm) resonated at higher field than that of the (2*S*,5*R*,1′*S*) isomer ($\delta = 5.48$ ppm) and the (2*S*,5*S*,1′*S*) isomer ($\delta = 5.21$ ppm). Similarly, the 2-furyl substituent at C-(1′) and the methyl group at C-(5) are *trans* to each other in the (2*S*,5*S*,1′*S*) and (2*S*,5*R*,1′*R*) isomers, while a *cis* relationship is seen for the (2*S*,5*R*,1′*S*) isomer. The C-(5)Me resonance of the (2*S*,5*R*,1′*S*) isomer absorbed at higher field ($\delta = 1.20$ ppm) with respect to that of the (2*S*,5*S*,1′*S*) isomer ($\delta = 1.37$ ppm) and (2*S*,5*R*,1′*R*) ($\delta = 1.43$ ppm). An identical trend was observed for the resonances of the C-(5)Me signals in ^{13}C NMR. It is also notable that the ^{1}H NMR signal for the C-(2) proton of the (2*S*,5*S*,1′*S*) isomer was seen within the narrow range of $\delta = 5.20$–5.21 ppm, which is typical of a number of relevant (2*S*,5*S*,1′*S*)-dioxolanone alcohols we have already synthesized.[8,10]

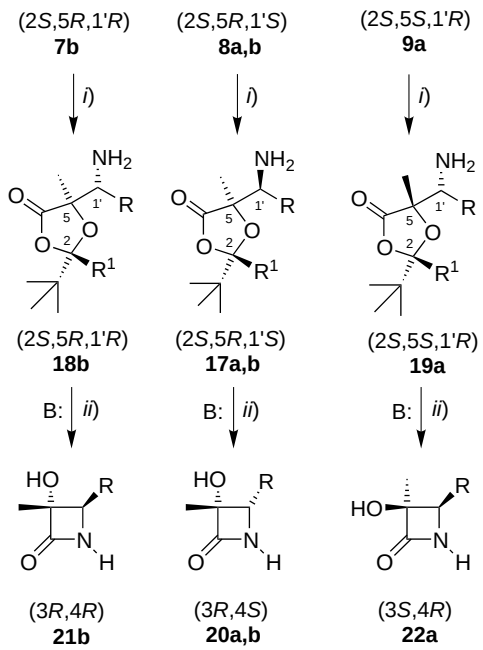
The azido dioxolanones **7**–**9** which were used as templates for the synthesis of methyl isoserinates (path **A** of Scheme 1, and Scheme 3) and β-lactams (path **B** of Scheme 1, and Scheme 4) were targets of this preliminary investigation. In particular, the β-lactam (3*R*,4*S*)-**20b** and the isoserinate (2*R*,3*S*)-**14**, are opportunely protected to be appended to taxoid derivatives according to standard methodologies. Regardless of the stereochemistry of the dioxolanone alcohol, the one-pot C-(1′) hydroxyl to azide conversion was achieved via zinc azide-mediated Mitsonobu azidation.[11] This protocol uses zinc azide (in the form of its more stable bis-pyridine complex) as the nucleophilic partner of the dioxolanone alcohol, electrophilically activated by the bis-*iso*-propylazodicarboxylate/Ph_3P system. The azidation of dioxolanone alcohols (2*S*,5*R*,1′*R*)-**5a**,**b** and (2*S*,5*S*,1′*S*)-**6a** occurred with inversion of configuration at the C-(1′) stereogenic center, yielding the 1′-azido dioxolanones (2*S*,5*R*,1′*S*)-**8a**, (2*S*,5*R*,1′*S*)-**8b** and (2*S*,5*S*,1′*R*)-**9a**, respectively. The azidation of (2*S*,5*R*,1′*R*)-**5a** also afforded the carbonate



i) MeO^-/MeOH; *ii*) H_2/Pd/C/Boc_2O; *iii*) H_2/Pd/C; *iv*) BzCl/$NaHCO_3$

8b, **13**: R = C_6H_5, R^1 = Me; **8a**, **12**: R = 2-furyl, R^1 = H

Scheme 3. Synthesis of isoserines from 1′-azido dioxolanones.



a: R= 2-Furyl, R^1 = H; **b**: R = C_6H_5, R^1= Me

i) H_2O/PPh_3; *ii*) B: = MeMgBr or LHMDS

Scheme 4. Synthesis of β-lactams from 1′-azido dioxolanones.

(2*S*,5*R*,1′*R*)-**10** (Fig. 2) (with a (2*S*,5*R*,1′*S*)-**8a**/(2*S*,5*R*,1′*R*)-**10** ratio of 1.7:1). The formation of this undesired side-product was substantially reduced to $\leq 5\%$ when bis-*iso*-propylazodicarboxylate was replaced by the more sterically demanding bis-*tert*-butylazodicarboxylate. Partial loss of selectivity at the C-(1′) stereocenter occurred during the azidation of the (2*S*,5*R*,1′*S*) diastereomers of **4a** and **4b**. In fact, the azidation of a (2*S*,5*R*,1′*S*)-**4a**/(2*S*,5*R*,1′*R*)-**5a** (9:1 mixture) gave a 3:1 mixture of (2*S*,5*R*,1′*R*)-**7a**/(2*S*,5*R*,1′*S*)-**8a**, (2*S*,5*R*,1′*S*)-**4b** gave a 12:1 mixture of azido derivatives (2*S*,5*R*,1′*R*)-**7b**/(2*S*,5*R*,1′*S*)-**8b** and the carbonate (2*S*,5*R*,1′*S*)-**11** (Fig. 2). The formation of this undesired side product was avoided when the azidation of (2*S*,5*R*,1′*S*)-**4b** was carried out with the bis-*tert*-butylazodicarboxylate/Ph_3P system.

The enantiomeric excess (e.e.) of all dioxolanone alcohols and 1′-azido dioxolanones (2*S*,5*R*,1′*S*)-**8a**,**b** and (2*S*,5*S*,1′*R*)-**9a** was determined by ^{1}H NMR analysis in the presence of the chiral shift reagent Yt(hfc)$_3$ and corresponded to the diastereomeric excess (d.e.) of the parent dioxolanones **1a** and **1b**. Namely, an e.e. of 94% was found for **4a**, **5a**, **6a**, **8a**, and **9a** and an e.e. of 86% was determined for **4b**, **5b**, **6b**, and **8b**.

2.1. Synthesis of isoserines

Methoxide-induced removal of the auxiliary of (2*S*,5*R*,1′*S*)-azido dioxolanones **8a** and **8b** (Scheme 3) gave the corresponding (2*R*,3*S*)-2-azido methyl esters **12** and **13**, respectively. Catalytic hydrogenation of (2*R*,3*S*)-**13** using Pd–C in the presence of bis-*tert*-butyldicarbonate (Boc_2O) gave the protected methyl isoserinate (2*R*,3*S*)-**15** which was already synthesized via an independent route.[12] This chemical correlation allowed the assignment of configuration of (2*S*,5*R*,1′*S*)-**8b**. Sequential catalytic hydrogenation of (2*R*,3*S*)-**12** and *N*-benzoylation under Schotten–Baumann conditions gave the methyl *N*-benzoylisoserinate (2*R*,3*S*)-**14**. 2,4-Dimethoxybenzylidene protection of (2*R*,3*S*)-**14** with 2,4-dimethoxybenzaldehyde dimethyl acetal[6b] in the presence of pyridinium toluene-*p*-sulfonate (PTS) in toluene at 110°C followed by LiOH induced hydrolysis afforded the oxazolidine carboxylic acid (2*R*,3*S*)-**16** as a 4:1 epimeric mixture, ready to be appended to taxoid derivatives.

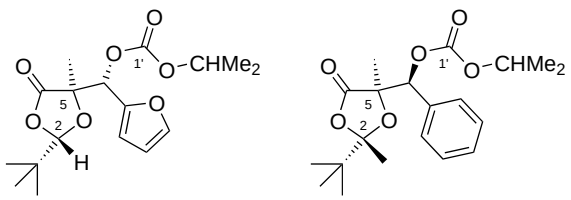


Figure 2. Carbonates (2*S*,5*R*,1′*R*)-**10** and (2*S*,5*R*,1′*S*)-**11**.

2.2. Synthesis of β-lactams (Scheme 4)

Catalytic hydrogenation of 1′-azido dioxolanones in the presence of Pd–C failed. Instead, (2*S*,5*R*,1′*S*)-**8a**,**b**, (2*S*,5*R*,1′*R*)-**7b**, and (2*S*,5*S*,1′*R*)-**9a** were reduced to the corresponding 1′-amino dioxolanones (2*S*,5*R*,1′*S*)-**17a**,**b**, (2*S*,5*R*,1′*R*)-**18b**, and (2*S*,5*S*,1′*R*)-**19a** with Ph_3P/H_2O.[13] The treatment of 1′-amino dioxolanones with bases caused the simultaneous cyclization and elimination of the acetal center with the formation of the corresponding β-lactams. Two bases were probed. Namely, the reaction of (2*S*,5*R*,1′*S*)-**17b** and MeMgBr under Birkofer's conditions[14] gave the β-lactam (3*R*,4*S*)-**20b**,[15] while the lithium bis(trimethylsilyl)amide (LHMDS) induced cyclization of (2*S*,5*R*,1′*R*)-**18b**, (2*S*,5*R*,1′*S*)-**17a**, and (2*S*,5*S*,1′*R*)-**19a**, yielded the β-lactams (3*R*,4*R*)-**21b**, (3*R*,4*S*)-**20a**, and (3*S*,4*R*)-**22a**, respectively. The analytical data for (3*R*,4*S*)-**20a**, and (3*R*,4*S*)-**20b** were consistent with the literature data[16] giving further proof of the configuration of the parent 1′-azido dioxolanones (2*S*,5*R*,1′*S*)-**17a** and **17b** and 1′-amino dioxolanones (2*S*,5*R*,1′*S*)-**8a** and **8b**. Similarly, the stereochemistry of (2*S*,5*R*,1′*R*)-**7b** and (2*S*,5*R*,1′*R*)-**18b** was further assessed via chemical correlation with the β-lactam (3*R*,4*R*)-**21b**.[16] Finally, the stereochemistry of 1′azido dioxolanone (2*S*,5*S*,1′*R*)-**9a** and 1′-amino dioxolanone (2*S*,5*S*,1′*R*)-**19a** was established via chemical correlation with the β-lactam (3*S*,4*R*)-**22a** whose ^{1}H and ^{13}C NMR spectral data were identical to those of its enantiomer (3*R*,4*S*)-**20a**.[16]

3. Conclusion

We have developed a route for the one step transformation of dioxolanone alcohols into 1′-azido dioxolanones. The conversion occurs with clean inversion of configuration at the 1′-position when a *cis* relationship exists between the C-(5) methyl group and the C-(1′) hydroxyl substituent, as in the (2*S*,5*R*,1′*R*) and (2*S*,5*S*,1′*S*) isomers. 1′-Azido dioxolanones are useful building blocks for the synthesis of other interesting compounds.[17] As an application, we have probed their potential as intermediates for the synthesis of isoserines and 1′-amino dioxolanones, from which β-lactams were synthesized. The synthesis of these important chiral intermediates is achieved in a few very simple steps and does not require the use of chiral auxiliaries or expensive protection/deprotection sequences with sterically hindered protecting groups in order to improve the diastereoselectivity.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer with Me_4Si or $CHCl_3$ (in $CDCl_3$) as internal standards. Mass spectra were recorded on an ion trap spectrometer with an ionization potential of 70 eV. Gas liquid chromatography (GC) was carried out on a

GC–mass spectrometer (ion trap, 70 eV). Infrared spectra were recorded on a Fourier-transform IR spectrometer. Preparative HPLC chromatography used an Hypersil column (10 μm CN CPS, 250×10.0 mm, *n*-hexane/MeOH, 88.5:1.5). Finally, a Chiracel OD column (Daicel 25×0.46 cm i.d.) was used for the enantioselective analysis of the 1′-amino-1,3-dioxolan-4-ones and β-lactams.

4.2. General procedure of synthesis of dioxolanone alcohols

A solution of the dioxolanone (1.0 equiv.) in THF was added to a cooled (−78°C) stirred solution of LDA (1.5 equiv.) and the mixture was stirred for 15 min at −78°C. The aldehyde (1.5–2.0 equiv.) was added. Unless otherwise stated, the reaction mixture was allowed to warm to −15°C with continuous stirring over a 3 h period. The reaction solution was quenched by the addition of saturated NH_4Cl solution (10 mL) and extracted with ethyl acetate. The extracts were combined, dried, and concentrated under reduced pressure. The diastereomeric composition of the dioxolanone alcohols was established directly in the crude reaction mixture by ^1H NMR. The mixture of dioxolanone alcohols was subjected to a first purification by flash chromatography on silica, which allowed the determination of overall yields. No variation of the product distribution was observed after this chromatography.

4.3. 2-*tert*-Butyl-5-(furan-2-yl-hydroxymethyl)-5-methyl-[1,3]-dioxolan-4-ones

The reaction of dioxolanone **1a** (1.0 g, 6.3 mmol) and furan-2-carbaldehyde **3** (0.91 g, 9.5 mmol) at −90°C over 90 min gave a 19:46:35 mixture of (2*S*,5*S*,1′*S*)-**6a**/(2*S*,5*R*,1′*R*)-**5a**/(2*S*,5*R*,1′*S*)-**4a**. (1.28 g, 5.04 mmol, 80%). Chromatography (SiO_2, *n*-pentane/Et_2O/EtOAc, 15.0:4.0:1.0) gave pure (2*S*,5*S*,1′*S*)-**6a** (0.13 g, 0.51 mmol) and a mixture of (2*S*,5*R*,1′*R*)-**5a** and (2*S*,5*R*,1′*S*)-**4a**. Recrystallization of the mixture from *n*-hexane gave pure (2*S*,5*R*,1′*R*)-**5a** (0.46 g, 1.82 mmol, 29%) and a mixture of (2*S*,5*R*,1′*S*)-**4a**/(2*S*,5*R*,1′*R*)-**5a** = 9:1 (0.40 g, 1.56 mmol, 25%). Alternatively, it was possible to separate the three stereoisomers by preparative HPLC column (Hypersil, 10 μm CN CPS, 250×10.0 mm, *n*-hexane/EtOH, 98.5:1.5); IR ($CDCl_3$, cm^{-1}): 3600–3500, 1789, 1484; MS (*m*/*z*): 254 (M^+), 210, 197, 168. Anal. calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.64; H, 6.96%.

(2*S*,5*S*,1′*S*)-**6a**: $[\alpha]_D^{20} = -12.5$ (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.84 (s, 9H), 1.50 (s, 3H), 2.70 (bs, 1H), 4.91 (s, 1H), 5.16 (s, 1H), 6.34 (m, 2H), 7.38 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 15.6, 23.3, 34.0, 71.1, 81.6, 108.1, 108.6, 110.5, 142.2, 150.8, 174.2.

(2*S*,5*R*,1′*R*)-**5a**: $[\alpha]_D^{20} = -4.72$ (*c* 0.53, $CHCl_3$); mp 99–100°C; ^1H NMR ($CDCl_3$): δ 0.93 (s, 9H), 1.49 (s, 3H), 2.70 (bs, 1H), 4.89 (s, 1H), 4.87 (s, 1H), 6.40 (m, 2H), 7.43 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 20.5, 23.3, 34.7, 72.2, 82.5, 108.4, 109.7, 142.2, 151.2, 172.9.

(2*S*,5*R*,1′*S*)-**4a**: ^1H NMR ($CDCl_3$): δ 0.96 (s, 9H), 1.36 (s, 3H), 2.70 (bs, 1H), 4.91 (s, 1H), 5.30 (s, 1H), 6.40 (m, 1H), 6.46 (m, 1H), 7.43 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 20.8, 23.5, 34.9, 72.3, 82.2, 109.4, 110.9, 111.1, 142.9, 151.8, 175.0.

4.4. General procedure for azidation of dioxolanone alcohols

A toluene solution of di-*iso*-propyl- or di-*tert*-butylazodicarboxylate was added to a stirred solution of the appropriate dioxolanone alcohol, PPh_3, and $ZnN_6{\cdot}2Py$ in toluene (10.0 mL) at 25°C. The mixture was sonicated, filtered on Celite, and the solvent was evaporated in vacuo. Flash chromatography (SiO_2, *n*-hexane/ethyl acetate) provided pure 1′-azido dioxolanones.

4.5. (2*S*,5*R*,1′*S*)-1′-(Azidophenylmethyl)-2-*tert*-butyl-2,5-dimethyl-[1,3]-dioxolan-4-one (2*S*,5*R*,1′*S*)-8b

Di-*iso*-propylazodicarboxylate (0.40 g, 2.0 mmol), PPh_3 (0.55 g, 2.1 mmol), (2*S*,5*R*,1′*R*)-**5b** (0.22 g, 0.8 mmol), and $ZnN_6{\cdot}2Py$ (0.24 g, 0.8 mmol) gave, after 3 h, (2*S*,5*R*,1′*S*)-**8b** (0.22 g, 0.72 mmol, 90%): mp 84–86°C; IR ($CDCl_3$, cm^{-1}): 2109, 1793; $[\alpha]_D^{20} = +163.8$ (*c* 0.6, $CHCl_3$); MS (*m*/*z*): 303 (M^+), 276, 245, 133, 115, 101, 77; ^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (s, 9H), 1.26 (s, 3H), 1.83 (s, 3H), 4.67 (s, 1H), 7.30–7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 22.2, 25.0, 39.0, 69.6, 81.9, 116.3, 128.5, 129.1, 129.3, 133.7, 173.7. Anal. calcd for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N 13.85. Found: C, 63.62; H, 6.79; N, 13.80%.

4.6. (2*S*,5*R*,1′*R*)-1′-(Azidophenylmethyl)-2-*tert*-butyl-2,5-dimethyl-[1,3]-dioxolan-4-one (2*S*,5*R*,1′*R*)-7b

Di-*tert*-butylazodicarboxylate (0.46 g, 2.0 mmol), PPh_3 (0.52 g, 2.0 mmol), (2*S*,5*R*,1′*S*)-**4b** (0.20 g, 0.72 mmol) and $ZnN_6{\cdot}2Py$ (0.24 g, 0.8 mmol) were reacted at 25°C for 24 h. Chromatography of the crude reaction mixture gave (2*S*,5*R*,1′*R*)-**7b** (0.10 g, 0.34 mmol, 47%) and (2*S*,5*R*,1′*S*)-**8b** (0.01 g, 0.03 mmol, 4.0%) and unreacted (2*S*,5*R*,1′*S*)-**4b** (0.07 g, 0.27 mmol). In another experiment (2*S*,5*R*,1′*S*)-**4b** (0.2 g, 0.72 mmol) was reacted with di-*iso*-propylazodicarboxylate (0.40 g, 2.0 mmol), PPh_3 (0.52 g, 2.0 mmol), and $ZnN_6{\cdot}2Py$ (0.24 g, 0.8 mmol) at 25°C for 15 h. Chromatography gave (2*S*,5*R*,1′*R*)-**7b** (0.12 g, 0.42 mmol, 58%), (2*S*,5*R*,1′*S*)-**8b** (0.012 g, 0.04 mmol, 6%) and the carbonate (2*S*,5*R*,1′*S*)-**11** (0.69 g, 0.19 mmol, 26%). (2*S*,5*R*,1′*R*)-**7b**: mp 97–99°C; IR ($CDCl_3$, cm^{-1}): 2110, 1790; $[\alpha]_D^{20} = -86.8$ (*c* 0.7, $CHCl_3$); MS (*m*/*z*): 303 (M^+), 276, 245, 133, 115, 101; ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 9H), 1.21 (s, 3H), 1.44 (s, 3H), 4.81 (s, 1H), 7.30–7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4, 22.5, 25.3, 39.2, 71.3, 82.5, 116.1, 128.9, 129.1, 129.3, 135.2, 173.0. Anal. calcd for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N 13.85. Found: C, 63.67; H, 7.12; N, 13.72%.

(2*S*,5*R*,1′*S*)-**7b**: IR ($CDCl_3$, cm^{-1}): 1810, 1755; $[\alpha]_D^{20} = +51$ (*c* 1.1, $CHCl_3$); MS (*m*/*z*): 364 (M^+), 307, 221, 179, 172, 133, 115, 105; ^1H NMR (400 MHz, $CDCl_3$): δ 1.01 (s, 9H), 1.18 (d, 3H, *J* = 6.4 Hz), 1.23 (d, 3H, *J* = 6.4

Hz), 1.30 (s, 3H), 1.84 (s, 3H), 4.76 (m, 1H), 5.59 (s, 1H), 7.37–7.40 (m, 3H), 7.40–7.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 21.7, 21.8, 21.9, 25.3, 39.2, 72.7, 80.6, 82.2, 116.6, 128.4, 129.1, 129.2, 134.8, 153.4, 173.7. Anal. calcd for $C_{20}H_{28}O_6$: C, 65.91; H, 7.74. Found: C, 65.57; H, 7.64%.

4.7. (2*S*,5*R*,1′*S*)-1′-(Azidofuran-2-yl-methyl)-2-*tert*-butyl-5-methyl-[1,3]-dioxolan-4-one (2*S*,5*R*,1′*S*)-8a

Di-*tert*-butylazodicarboxylate (0.46 g, 2.0 mmol), PPh_3 (0.55 g, 2.1 mmol), (2*S*,5*R*,1′*R*)-**5a** (0.23 g, 0.83 mmol), and $ZnN_6{\cdot}2Py$ (0.24 g, 0.8 mmol) gave, after 20 h, (2*S*,5*R*,1′*S*)-**8a** (0.18 g, 0.65 mmol, 78%). In another experiment (2*S*,5*R*,1′*R*)-**5a** (0.23 g, 0.83 mmol) was reacted with di-*iso*-propylazodicarboxylate (0.4 g, 2.0 mmol), PPh_3 (0.55 g, 2.1 mmol), and $ZnN_6{\cdot}2Py$ (0.24 g, 0.8 mmol) in 15 h. Chromatography gave (2*S*,5*R*,1′*S*)-**8a** (0.13 g, 0.45 mmol, 54%) and the carbonate derivative (2*S*,5*R*,1′*R*)-**10** (0.09 g, 0.27 mmol, 33%). (2*S*,5*R*,1′*S*)-**8a**: IR ($CDCl_3$, cm^{-1}): 2142; $[\alpha]_D^{20}=-1.98$ (*c* 0.53, $CHCl_3$); MS (*m*/*z*): 279 (M^+), 237, 183, 167, 149, 94; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (s, 9H), 1.35 (s, 3H), 4.80 (s, 1H), 5.40 (s, 1H), 6.40 (m, 1H), 6.60 (m, 1H), 7.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 23.5, 35.0, 63.4, 81.6, 110.9, 111.0, 111.1, 143.8, 147.5, 173.8. Anal. calcd for $C_{13}H_{17}N_3O_4$: C, 55.91; H, 6.14, N, 15.05. Found: C, 55.54; H, 6.29; N, 14.68%.

(2*S*,5*R*,1′*R*)-**10**: IR ($CDCl_3$, cm^{-1}): 2980, 1806, 1756; MS (*m*/*z*): 340 (M^+), 283, 172; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (s, 9H), 1.30 (d, 3H), 1.33 (d, 3H), 1.48 (s, 3H), 4.90 (m, 1H, $J=6.4$ Hz), 4.95 (s, 1H), 5.85 (s, 1H), 6.38 (m, 1H), 6.52 (m, 1H), 7.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.6, 21.7, 21.8, 23.3, 34.7, 73.0, 75.4, 80.6, 109.6, 110.0, 110.1, 142.8, 147.6, 153.2, 171.5. Anal. calcd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11. Found: C, 59.74; H, 7.28%.

4.8. (2*S*,5*R*,1′*R*)-1′-(Azidofuran-2-yl-methyl)-2-*tert*-butyl-5-methyl-[1,3]-dioxolan-4-one (2*S*,5*R*,1′*R*)-7a

Di-*tert*-butylazodicarboxylate (0.41 g, 1.8 mmol), PPh_3 (0.50 g, 1.9 mmol), $ZnN_6{\cdot}2Py$ (0.23 g, 0.75 mmol), and a (2*S*,5*R*,1′*S*)-**4a**/(2*S*,5*R*,1′*R*)-**5a** (9:1 mixture; 0.19 g, 0.75 mmol) at 15°C in 10 h gave, after chromatography, a (2*S*,5*R*,1′*R*)-**7a**/(2*S*,5*R*,1′*S*)-**8a** = 2.8:1 mixture (0.13 g, 0.48 mmol, 64%) and unreacted (2*S*,5*R*,1′*S*)-**4a** (0.02 g, 0.08 mmol). (2*S*,5*R*,1′*S*)-**8a**: IR ($CDCl_3$, cm^{-1}): 2140; MS (*m*/*z*): 279 (M^+), 237, 183, 167, 149, 94; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (s, 9H), 1.51 (s, 3H), 4.67 (s, 1H), 4.97 (s, 1H), 6.42 (m, 1H), 6.51 (m, 1H), 7.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 23.4, 34.9, 64.0, 82.1, 110.1, 110.7, 111.2, 143.5, 147.9, 172.5. Anal. calcd for $C_{13}H_{17}N_3O_4$: C, 55.91; H, 6.14; N, 15.05. Found: C, 56.42; H, 6.20; N, 15.35%.

4.9. (2*S*,5*S*,1′*R*)-1′-(Azidofuran-2-yl-methyl)-2-*tert*-butyl-5-methyl-[1,3]-dioxolan-4-one (2*S*,5*S*,1′*R*)-9a

Di-*tert*-butylazodicarboxylate (0.23 g, 1.00 mmol), PPh_3 (0.26 g, 1.0 mmol), (2*S*,5*S*,1′*S*)-**6a** (0.10 g, 0.41 mmol), and $ZnN_6{\cdot}2Py$ (0.12 g, 0.41 mmol) at 15°C over 8 h gave (2*S*,5*S*,1′*R*)-**9a** (0.18 g, 0.65 mmol, 65%). IR ($CDCl_3$, cm^{-1}): 2142; $[\alpha]_D^{20}=-138$ (*c* 0.6, $CHCl_3$); MS (*m*/*z*): 279 (M^+), 237, 183, 167, 149, 94; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (s, 9H), 1.31 (s, 3H), 4.75 (s, 1H), 5.20 (s, 1H), 6.40 (m, 1H), 6.53 (m, 1H), 7.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.6, 23.8, 34.5, 61.9, 81.7, 108.2, 111.0, 111.3, 143.8, 147.1, 173.14. Anal. calcd for $C_{13}H_{17}N_3O_4$: C, 55.91; H, 6.14; N, 15.05. Found: C, 55.54; H, 6.31; N, 14.60%.

4.10. (2*R*,3*S*)-3-Azido-2-hydroxy-2-methyl-3-phenylpropionic acid methyl ester (2*R*,3*S*)-13

A solution of (2*S*,5*R*,1′*S*)-**8b** (0.27 g, 0.9 mmol) in MeOH (2.0 mL) and a solution of MeONa (0.1 M, 3.0 mL 0.30 mmol) was stirred at 60°C under argon for 45 min. The reaction mixture was diluted with saturated NH_4Cl solution (5.0 mL) and extracted with EtOAc. The organic solvent was dried and evaporated to obtain of (2*R*,3*S*)-**13** (0.18 g, 0.76 mmol, 85%): IR ($CDCl_3$, cm^{-1}): 2109, 1739; $[\alpha]_D^{20}=+114.5$ (*c* 0.7, $CHCl_3$); MS (*m*/*z*): 235 (M^+), 208, 193, 158, 148, 133, 106; ^{1}H NMR (400 MHz $CDCl_3$): δ 1.17 (s, 3H), 3.59 (b, 1H), 3.87 (s, 3H), 4.71 (s, 1H), 7.3–7.5 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.8, 53.3, 70.8, 76.8, 128.5, 129.0, 129.3, 133.9, 175.5. Anal. calcd for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 55.94; H, 5.68; N, 17.72%.

4.11. (2*R*,3*S*)-3-(*tert*-Butoxycarbonylamino)-2-hydroxy-2-methyl-3-phenylpropionic acid methyl ester (2*R*,3*S*)-15

An ethyl acetate solution (3.0 mL) of (2*R*,3*S*)-**13** (0.04 g, 0.17 mmol), di-*tert*-butyldicarbonate (0.05 g, 0.28 mmol), and Pd–C (5%, 0.005 g) was stirred under hydrogen (balloon pressure) for 48 h. The reaction mixture was filtered through Celite, the solvent evaporated and the residue chromatographed (SiO_2, *n*-hexane/ethyl acetate, 5:1) to afford (2*R*,3*S*)-**15** (0.04 g, 0.14 mmol, 80%) whose analytical data were consistent with those reported in the literature.[6b] (2*R*,3*S*)-**15**: IR ($CDCl_3$, cm^{-1}): 3500, 2970, 1730; $[\alpha]_D^{20}=-5.5$ (*c* 0.7, $CHCl_3$); MS (*m*/*z*): 310 (MH^+), 271, 254, 210, 193, 105; ^{1}H NMR (400 MHz $CDCl_3$): δ 1.19 (s, 3H), 1.38 (s, 9H), 3.54 (b, 1H), 3.84 (s, 3H), 4.95 (d, 1H, $J=10$ Hz), 5.48 (d, 1H), 7.3–7.35 (m, 5H) [lit.:[6b] 1.20, 1.38, 3.51, 3.84, 4.95, 5.45, 7.28–7.35]; ^{13}CNMR (100 MHz, $CDCl_3$): δ 29.9, 28.5, 53.6, 59.9, 79.9, 128.1, 128.5, 128.7, 137.9, 155.0, 176.9. Anal. calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 61.94; H, 7.58; N, 4.72%.

4.12. (2*R*,3*S*)-3-Azido-3-furan-2-yl-2-hydroxy-2-methyl-propionic acid methyl ester (2*R*,3*S*)-12

A MeOH (4.0 mL) solution of (2*S*,5*R*,1′*S*)-**8a** (0.86 g, 3.1 mmol) and 6.2 mL of 1.0 M solution of MeONa (6.2 mmol) was stirred at 50°C under argon for 2 h. The reaction mixture was diluted with 5.0 mL of saturated NH_4Cl solution and extracted with ethyl acetate. The extract was dried and concentrated under reduced pressure to obtain (2*R*,3*S*)-**12** (0.88 g, 0.29 mmol, 95%).

IR ($CDCl_3$, cm^{-1}): 2110, 1739; $[\alpha]_D^{20}=+86.0$ (*c* 1.0, $CHCl_3$); MS (*m*/*z*): 225 (M^+), 183, 147, 129, 111, 83; ^1H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 3H), 3.52 (s, 1H), 3.87 (s, 3H), 4.69 (s, 1H), 6.40 (m, 1H), 6.60 (m, 1H), 7.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.1, 53.7, 63.9, 77.4, 110.9, 111.0, 143.4, 147.9, 175.3. Anal. calcd for $C_9H_{11}N_3O_4$: C, 48.00; H, 4.92; N, 18.66. Found: C, 48.26; H, 4.79; N, 18.48.

4.13. (2*R*,3*S*)-3-Benzoylamino-3-furan-2-yl-2-hydroxy-2-methylpropionic acid methyl ester (2*R*,3*S*)-14

An ethyl acetate solution (10.0 mL) of (2*R*,3*S*)-**12** (0.88 g, 2.9 mmol) and 0.12 g of 5% Pd–C was stirred under hydrogen for 15 h. After the reaction mixture was filtered and mixed with ethyl acetate (10 mL) and saturated $NaHCO_3$ solution (10 mL), benzoyl chloride (0.42 g, 3.0 mmol) was added over 10 min. The organic phase was separated and the aqueous phase was extracted with ethyl acetate. The combined organic phase was extracted with brine, dried and concentrated under reduced pressure to obtain (2*R*,3*S*)-**14** (0.70 g, 2.3 mmol, 80%). IR ($CDCl_3$, cm^{-1}): 1730; $[\alpha]_D^{20}=-3.76$ (*c* 1.38, $CHCl_3$); MS (*m*/*z*): 303 (M^+), 288, 198; ^1H NMR (400 MHz, $CDCl_3$): δ 1.41 (s, 3H), 3.67 (bs, 1H), 3.81 (s, 3H), 5.68 (d, 1H), 6.35 (m, 1H), 6.43 (m, 1H) 7.01 (d, 1H), 7.4–7.8 (m, 6H, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ relevant resonances): δ 23.2, 53.0, 53.4, 76.6, 109.1, 110.2, 166.4, 175.3. Anal. calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 62.62; H, 5.88; N, 4.50%.

4.14. Methyl (2*S*,3*R*)-3-Benzoyl-2-(2,4-dimethoxyphenyl)-4-furan-2-yl-5-methyloxazolidine-5-carboxylate (2*R*,3*S*)-16

A mixture of (2*R*,3*S*)-**14** (0.43 g, 1.42 mmol), 1-dimethoxymethyl-2,4-dimethoxybenzene (0.61 g, 2.85 mmol), and pyridinium toluene-*p*-sulfonate (0.04 g, 0.15 mmol) in toluene (15 mL) was refluxed for 1 h. The solvent was evaporated, the residue was dissolved in CH_2Cl_2 and extracted with water. The organic phase was dried. Evaporation of the solvent and chromatography (SiO_2, CH_2Cl_2/EtOAc, 29:1) gave **16** (0.56 g, 1.24 mmol, 75%) as a 4:1 epimeric mixture. IR ($CDCl_3$, cm^{-1}): 2980–2900, 1735, 1700; MS (*m*/*z*): 451 (M^+), 392, 286, 285, 267, 165; ^1H NMR (major diastereoisomer) (400 MHz, $CDCl_3$): δ 1.15 (s, 3H, Me), 3.73 (s, 6H, OMe), 3.80 (s, 3H, OMe), 6.22 (bs, 1H), 6.32 (bs, 1H), 6.35 (m, 1H), 6.42 (m, 1H), 6.68 (s, 1H), 7.10–7.25 (bs, 4H), 7.20–7.35 (bs, 1H), 7.42 (s, 1H), 7.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.6, 29.9, 53.4, 55.6, 56.0, 61.4, 85.6, 98.6, 104.6, 110.6, 110.8, 117.8, 127.2, 128.2, 128.9, 130.4, 136.1, 142.9, 151.5, 159.4, 161.8, 173.2, 173.3. ^1H NMR (minor diastereoisomer) (400 MHz, DMSO, 55°C): δ 1.15 (bs, 3H, Me), 3.43 (s, 3H, OMe), 3.65–3.85 (bs, 6H, 2 OMe), 5.8–5.9 (bs, 1H), 6.25–6.38 (bs, 1H), 6.40–6.58 (bs, 2H), 6.80 (s, 1H), 6.9–7.10 (bs, 1H), 7.20–7.40 (bs, 5H), 7.57 (b, 1H). Anal. calcd for $C_{25}H_{25}NO_7$: C, 66.51; H, 5.58; N, 3.10. Found: C, 66.85; H, 5.72; N, 3.38%.

4.15. General procedure for the reduction of 1′-azido dioxolanones to 1′-amino dioxolanones by using Ph_3P/H_2O

The 1′-azido dioxolanone (1.0 equiv.) and Ph_3P (1.5 equiv.), in the presence of few drops of H_2O, was heated at 60°C in THF. After addition of ethyl ether, the reaction mixture was extracted three times with 1.0 N aqueous HCl. The aqueous solution was washed with ethyl ether. The aqueous phase was treated with solid $NaHCO_3$ and extracted with EtOAc. The organic layer was dried over Na_2SO_4, the solvent evaporated under reduced pressure and chromatographed (SiO_2, *n*-hexane/ethyl acetate, 1:1) to afford the corresponding 1′-amino dioxolanone.

4.16. (2*S*,5*R*,1′*S*)-1′-(Aminophenylmethyl)-2-*tert*-butyl-2,5-dimethyl-[1,3]-dioxolan-4-one (2*S*,5*R*,1′*S*)-17b

The 1′-azido dioxolanone (2*S*,5*R*,1′*S*)-**8b** (0.25 g, 0.83 mmol) gave the 1′-amino dioxolanone (2*S*,5*R*,1′*S*)-**17b** (0.21 g, 0.75 mmol, 90%). IR ($CDCl_3$, cm^{-1}): 3500–3400, 1780; $[\alpha]_D^{20}=+49.0$ (*c* 0.7, $CHCl_3$); MS (*m*/*z*): 277 (M^+), 263, 220, 132, 106, 91, 79; ^1H NMR ($CDCl_3$): δ 1.02 (s, 9H, 3 Me), 1.28 (s, 3H, Me), 1.76 (s, 3H, Me), 4.07 (s, 1H, H–C–N), 7.25–7.45 (m, 5H, arom.); ^{13}C NMR ($CDCl_3$): δ 22.3, 22.4, 25.1, 39.0, 61.2, 84.0, 115.5, 127.7, 127.9, 128.3, 141.2, 175.5. Anal. calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.50; H, 8.49; N, 4.82%.

4.17. (3*R*,4*S*)-4-Phenyl-3-hydroxy-3-methylazetidin-2-one (3*R*,4*S*)-20b

An ethereal solution of MeMgBr (3.0 M, 2.4 mmol) was added to an ethereal solution of (2*S*,5*R*,1′*S*)-**17b** (0.21 g, 0.75 mmol) at 0°C. The mixture was stirred at 25°C for 60 min. The reaction was quenched with a saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, and the solvent evaporated under reduced pressure. Chromatography of the residue (SiO_2, EtOAc/*n*-hexane, 2:1) gave (3*R*,4*S*)-**20b** (0.11 g, 0.61 mmol, 81%) with analytical data consistent with those reported in the literature.[1d,6c] (3*R*,4*S*)-**20b**: mp 171–173°C; IR ($CDCl_3$, cm^{-1}): 3650–3400, 1771; $[\alpha]_D^{20}=+101$ (*c* 0.5, CD_3COCD_3); MS (*m*/*z*): 177 (M^+), 134; 106; ^1H NMR (CD_3COCD_3): δ 0.89 (s, 3H), 2.75–2.85 (b, 1H), 4.64 (s, 1H), 7.20–7.60 (m, 6H); ^{13}C NMR (CD_3COCD_3): δ 22.7, 65.6, 86.8, 128.2, 128.8, 139.1, 172.1. Anal. calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N 7.90. Found: C, 68.04; H, 6.44; N, 8.05%.

4.18. (2*S*,5*R*,1′*R*)-1′-(Aminophenylmethyl)-2-*tert*-butyl-2,5-dimethyl-[1,3]-dioxolan-4-one (2*S*,5*R*,1′*R*)-18b

The 1′-azido dioxolanone (2*S*,5*R*,1′*R*)-**7b** (0.13 g, 0.44 mmol) gave, after 18 h, the 1′-amino dioxolanone (2*S*,5*R*,1′*R*)-**18b** (0.11 g, 0.39 mmol, 88%). IR ($CDCl_3$, cm^{-1}): 3500–3400, 1780; $[\alpha]_D^{20}=+51.0$ (*c* 0.5, $CHCl_3$); MS (*m*/*z*): 277 (M^+), 263, 220, 132, 106, 91, 79; ^1H NMR ($CDCl_3$): δ 0.97 (s, 9H), 1.42 (s, 3H), 1.47 (s, 3H), 4.39 (s, 1H), 7.30–7.45 (m, 5H); ^{13}C NMR

($CDCl_3$): δ 18.8, 23.0, 24.9, 38.8, 60.5, 82.1, 115.1, 127.9, 128.3, 128.5, 139.5, 175.2. Anal. calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N 5.05. Found: C, 69.44; H, 8.24; N, 5.15%.

4.19. (3*R*,4*R*)-4-Phenyl-3-hydroxy-3-methylazetidin-2-one (3*R*,4*R*)-21b

A solution of (2*S*,5*R*,1′*R*)-**18b** (0.07 g, 0.25 mmol) in THF (2.0 mL) was added at −50°C to a stirred THF solution (4 mL) of LHMDS (1.8 equiv.). The reaction mixture was allowed to warm to −25°C with continuous stirring over 3 h. The reaction solution was quenched by the addition of acetic acid, concentrated under reduced pressure. Chromatography of the residue (SiO_2, EtOAc/*n*-hexane, 2:1) gave the β-lactam (3*R*,4*R*)-**21b** (0.04 g, 0.23 mmol, 91%) whose analytical data are consistent with those reported in the literature.[1d] (3*R*,4*R*)-**21b**: mp 191–193°C; IR ($CDCl_3$, cm^{-1}): 3650–3400, 1771; $[\alpha]_D^{20}=-37.5$ (*c* 0.5, CD_3COCD_3); MS (*m*/*z*): 177 (M^+), 134; 106; ^1H NMR (CD_3COCD_3): δ 0.90 (s, 3H), 2.85–2.90 (b, 1H), 4.64 (s, 1H), 7.20–7.45 (m, 5H), 7.60 (b, 1H); ^{13}C NMR (CD_3COCD_3): δ 19.0, 66.3, 88.0, 126.8, 128.3, 129.3, 139.2, 172.3. Anal. calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N 7.90. Found: C, 67.43; H, 6.10; N, 7.75%.

4.20. (3*R*,4*S*)-4-Furan-2-yl-3-hydroxy-3-methylazetidin-2-one (3*R*,4*S*)-20a

The 1′-azido dioxolanone (2*S*,5*R*,1′*S*)-**8a** (0.26 g, 0.92 mmol) was reduced using the Ph_3P/H_2O reduction protocol to yield the corresponding 1′-amino dioxolanone (2*S*,5*R*,1′*S*)-**17a**. The solution of crude (2*S*,5*R*,1′*S*)-**17a** in 4.0 mL of THF was added at −50°C to a stirred THF solution (8 mL) of 1.1 mmol of LHMDS. The reaction temperature was raised to −25°C with continuous stirring over 2 h. The reaction solution was quenched by the addition of acetic acid and concentrated under reduced pressure. Chromatography of the residue (SiO_2, EtOAc/*n*-hexane, 2:1) gave (3*R*,4*S*)-**20a** (0.10 g, 0.57 mmol, 62%) which has analytical data consistent with those reported in the literature.[1c] (3*R*,4*S*)-**20a**: mp 127–129°C; $[\alpha]_D^{22}=+70$ (*c* 0.3, CH_3COCH_3); ^1H NMR ($CDCl_3$): δ 1.64 (s, 3H), 2.90–3.00 (br s, 1H), 4.62 (s, 1H), 6.30–6.45 (m, 2H), 6.60–6.70 (br s, 1H), 7.45–7.50 (m, 1H). Anal. calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.32; H, 5.38; N, 8.46%.

4.21. (3*S*,4*R*)-4-Furan-2-yl-3-hydroxy-3-methylazetidin-2-one (3*S*,4*R*)-22a

The β-lactam (3*S*,4*R*)-**22a** was prepared in 54% yields from the 1′-azido dioxolanone (2*S*,5*S*,1′*R*)-**9a** under identical conditions reported in Section 4.20. The compound showed identical properties to its enantiomer (3*R*,4*S*)-**20a** except for the sign of the optical rotation: $[\alpha]_D^{20}=-70.6$ (*c* 0.4, CH_3COCH_3).

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4. Ojima, I.; *Acc. Chem. Res.* **1995**, *28*, 383–389. According to this protocol the carbonyl group of an *N*-unsubstituted β-lactam is coupled to the amino group of an amino acid after acylation of the nitrogen atom of the β-lactam.
5. Structure–activity relationship (SAR) studies have shown that taxoids bearing an additional methyl substituent at C-(2) of the (2′*R*,3′*S*)-α,α-disubstituted isoserine appendant display higher cytotoxic activity compared to the parent docetaxel and paclitaxel when evaluated in vitro assays. See: Kant, J.; Schwartz, W. S.; Fairchild, C.; Gao, Q.; Huang, S.; Long, B. H.; Kadow, J. F.; Langley, D. R.; Farina, V.; Vyas, D. *Tetrahedron Lett.* **1996**, *37*, 6495–6498.
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7. The azidation of the C-(1′)-OH group can also be carried out in a two step process which involves the conversion of the C-(1′)-OH into a bromide followed by azidation. The net result is retention of configuration.
8. The enolates **1a** (2*S*/2*R*=97:3) and **1b** (2*S*:2*R*=93:7) were obtained by treatment of the corresponding (2*S*,5*S*)/(2*R*,5*S*)=97:3 and (2*S*,5*S*)/(2*R*,5*S*)=93:7 mixtures of 2-*tert*-butyl-2,5-dimethyl-[1,3]-dioxolan-4-one and 2-*tert*-butyl-5-methyl-[1,3]-dioxolan-4-one, respectively, with lithium di-*iso*-propylamide (LDA). See: Battaglia, A.; Barbaro, G.; Giorgianni, P.; Guerrini, A.; Bertucci, C.; Geremia, S. *Chem. Eur. J.* **2000**, *6*, 3551–3557.
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15. The chiral β-lactam (3*R*,4*S*)-**20b** was used, after protection of the 3-hydroxyl group with TESCl and *N*-acylation, as the key intermediate to append to 7-TES baccatin III. See: Ref. 5.
16. The independent synthesis of β-lactams (3*R*,4*S*)-**20a**,**b** and (3*R*,4*R*)-**21a**,**b** was achieved via addition reactions of (2*S*)-enolates of dioxolanones **1a**,**b** to phenyltrimethylsilylimine[1d] and 2-furyltrimethylsilylimine.[1c] The synthesis of (3*R*,4*S*)-**20b** is also reported in Ref. 6c.
17. For example, it is possible to transform the azido group in other interesting functional groups, such as N=C=O, N=C=S, and N=S=O.