(*3R*)-Chiral Control of 3-Alkyl-3-hydroxy-*β*-lactams via Addition Reaction of Imines to Enolates of 1,3-Dioxolan-4-ones†

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A method is described for the chiral construction of (*3R*)-3-alkyl-3-hydroxy-*β*-lactams in a versatile and predictable manner. This protocol follows Seebach's synthetic principle of self-regeneration of stereocenters and has been applied to addition reactions among a selected number of imines and (*2S*)-chiral enolates of 1,3-dioxolan-4-ones. These reagents are easily available from the acetalization of (*S*)-α-hydroxy acids (lactic, mandelic, isovaleric, malic) and pivalaldehyde or pinacolone. In several cases, the addition of the enolate to the imine, the cyclization, and the removal of the auxiliary center occur in a one-step sequence, affording the corresponding *β*-lactams as (*3R,4S*)-*Z* and (*3R,-4R*)-*E* diastereomeric mixtures with high enantiomeric excesses. Four N-unsubstituted (*3R,4S*)-3-hydroxy-3-methyl-*β*-lactams bearing 2-furyl (**4e**), phenylethenyl (**4h**), methoxycarbonyl (**4i**), and 2-thienyl (**4l**) substituents at C4 were obtained as major diastereomers and were purified by crystallization. The simultaneous presence of these substituents at C3 and C4 make these *β*-lactams useful intermediates for the synthesis of new taxoids with interesting structural modifications at the isoserine moiety.

Introduction

The development of new approaches to the stereocontrolled synthesis of *β*-lactam intermediates has been a subject of interest in the context of their possible use as biologically active compounds or as versatile chiral building blocks. Biologically active targets are, for example, the *β*-lactam antibiotics[1] or the inhibitors of cholesterol absorption,[2] while the potential usefulness of *β*-lactams as synthons has been evidenced by the development of the "*β*-lactam synthon method".[3]

Several methods for the synthesis of 3,4-disubstituted *β*-lactams are now available. In particular, the addition of imines to ketenes[4] or to ester enolates[5] has acquired significant importance for the asymmetric synthesis of the azetidinone ring.[1a,6] Alternatively, precursors from the "chiral pool" for the synthesis of *β*-lactams are, for example, *β*-amino acids,[7] *β*-amino esters,[8] *β*-halo amides,[9] and *β*-hydroxy amides.[10] However, methods for the construction of *β*-lactams with quaternary stereogenic centers are still scarce. A few methods have been developed for creating quaternary stereogenic centers at the C4 and the C3 position.[11] These reactions are directed toward the synthesis of 3-heterosubstituted *β*-lactams, such as 3-alkyl-3-hydroxy-*β*-lactams and 3-alkyl-3-amino-

† This paper is dedicated to the memory of Prof. Gaetano Maccagnani on the tenth anniversary of his death.

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(3) For instance, the cleavage of the *β*-lactam ring at the N−C(O) bond affords a variety of protein and nonprotein amino acids and peptides of biological and medicinal interest, while the reductive cleavage of the *β*-lactam ring affords alkanoic acid derivatives, such as α-hydroxy- and α-amino acids. Other types of reactions specifically involve the C=O functionality. Among various possibilities, it is worth mentioning the chemoselective alkylation with Grignard reagents or with cuprates yielding *β*-amino ketones and the selective reduction with alanes, which provide a useful protocol of synthesis of azetidines. Selected references: (a) Ojima, I. In *The Organic Chemistry of β-Lactams and β-Lactam Antibiotics*; Georg, G. I., Ed.; VCH: New York, 1992; Chapter 4, pp 197−255. (b) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383−389 and references therein. (c) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377−386. (d) Ojima, I.; Suga, S.; Abe, R. *Chem. Lett.* **1980**, 853−856. (e) Ojima, I.; Shimizu, N. *J. Am. Chem. Soc.* **1986**, *108*, 3100−3102. (f) Palomo, C.; Aizpurua, J. M.; Garcia, J. M.; Iturburu, M.; Odriozola, J. M. *J. Org. Chem.* **1994**, *59*, 5184−5188. (g) Spero, D. M.; Kapadia, S.; Farina, V. *Tetrahedron Lett.* **1995**, *36*, 4543−4546. (h) Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K. *J. Org. Chem.* **1991**, *56*, 5263−5277.

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β-lactams, by photoaddition of chromium-alkoxy-carbene complexes to optically active imines[12] or by stereospecific addition of diphenylnitrone to the enantiomerically pure (*3S*,*4R*)-3-hydroxy-3-methyl-4-furyl azetidinone.[13] Stereospecific α-alkylation of 3-amino- and 3-alkoxy-C3,C4-disubstituted-β-lactams following Ojima's protocol have also been reported.[3a,b] Because of the importance of trisubstituted β-lactams bearing heterosubstituents at a C3 quaternary stereogenic center, both as substrates for the "β-lactam synthon method" and for studies of biological activity, we started to develop a new synthetic protocol of their chiral construction in a versatile and predictable manner. For this purpose, we believe that α-heterosubstituted carboxylic acids, like α-hydroxy, α-mercapto, and α-amino acids, are inexpensive natural chiral pools that could be used for the synthesis of trisubstituted β-lactams with absolute stereocontrol at the C3 quaternary center bearing interesting functional groups, such as OR, SR, and NHR. This is very important since the biological activity of the β-lactams depends on the type of substituent and is prevalently exhibited by one of the enantiomers. Palomo[11a] clearly pointed out the importance of understanding the reactivity of 4,4-disubstituted β-lactams to provide new opportunities for studying structure−activity relationships and for the designing new antibiotics and/or enzyme inhibitors. This necessity has clearly been supported by some experimental findings, i.e. the superior activity of the 4,4-disubstituded β-lactam tigemonam[14] by the Squibb group over other oral β-lactam antibiotics. Similar support has also been found in the case of 3,3-disubstituted β-lactams. Indeed, the presence of a 3-methoxy substituent as part of a quaternary stereogenic center at the C3 carbon atom of the 3-methoxy-3-amino-monobactamic acid increases the β-lactamase stability with respect to the C3-monosubstituted-3-amino-monobactamic acid.

As our first target, we selected the 3-hydroxy-β-lactams, efficient carboxylate mimics,[15] that are present in pharmacologically active monobactams, such as Sulfazecin and related products,[16] and in enzyme inhibitors, such as the tabtoxinine-β-lactam and its analogues.[17] Moreover, these compounds with correct absolute configurations serve as precursors to the corresponding α-hydroxy-β-amino acids (isoserines), which are key components of a large number of therapeutically important compounds. As an example, (*2R*,*3S*)-3-amino-2-hydroxy-5-methylhexanoic acid (norstatine) and (*3R*,*4S*)-4-amino-3-hydroxy-5-methylheptanoic acid (statine) are residues for peptide inhibitors of enzymes, such as renin[18] and HIV-1 protease.[19] Furthermore, phenylisoserine analogues are used to synthesize new taxoids.[20] To achieve the goal of full control of stereochemistry at the C3-alkyl-C3-hydroxy quaternary center, we have devised a protocol that employs imines as the electrophilic partners of enolates of acetal-type derivatives. This strategy follows the synthetic principle called "self-regeneration of stereocenters", developed by Seebach,[21] which has been used for EPC[22] alkylations and aldol condensations to chiral cyclic enolates. In particular, the present paper focuses on the applicability of this protocol for the addition reactions of lithium enolates of dioxolan-4-ones, derived from the condensation of α-hydroxy-substituted carboxylic acids with pivalaldehyde or pinacolone, to imines.

Results and Discussion

Reactions of the Enolates of Dioxolanones Derived from Pivalaldehyde to Imines. The role of peripheral substituents in the dioxolanones derived from pivalaldehyde was studied using the diphenylimine **1** as the non-enolizable partner and the (2*S*,5*S*)-2-(*tert*-butyl)-5R-substituted-1,3-dioxolan-4-ones (**2a**−**d**) (Figure 1) derived from the acetalization of (*S*)-lactic, (*S*)-mandelic, (*S*)-α-hydroxy-isovaleric, and (*S*)-malic acids. These lactones can be obtained as pure homochiral material via fractional crystallization at low temperatures. However, suitable acetalization protocols are available which allow their synthesis with an excellent selectivity of cyclization. So far, compounds **2a**−**d** were obtained, and directly

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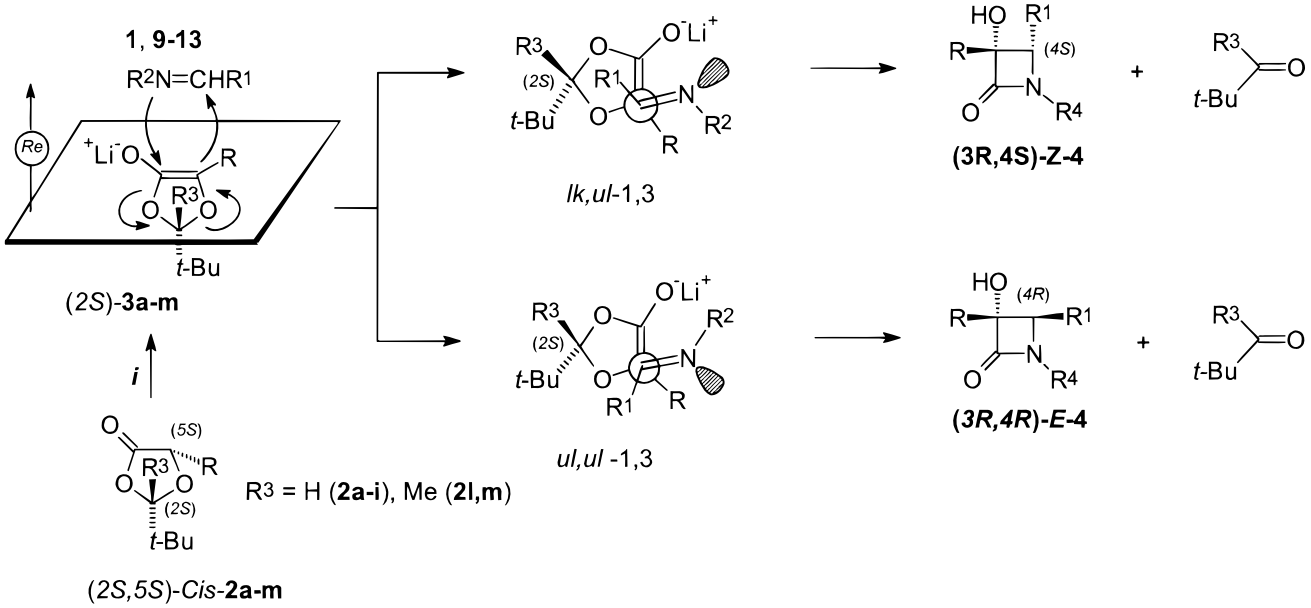
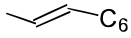
Scheme 1. Formation of β-lactams 4a−m via Addition Reactions of Enolates of Dioxolanones (2*S*)-3a−f to Imines 1 and 8−12



1, 2a, 4a: R = Me, $R^1 = R^2 = R^4 = C_6H_5$; **1, 2b, 4b**: R = $R^1 = R^2 = R^4 = C_6H_5$; **1, 2c, 4c**: R = Me_2CH, $R_1 = R^2 = R^4 = C_6H_5$;
1, 2d, 4d: R = CH_2COOH, $R^1 = R^2 = R^4 = C_6H_5$; **8, 2e, 4e**: R = Me, R^1 = 2-furyl, $R^2 = Me_3Si$, R^4 = H;
9, 2f, 4f: R = Me, $R^1 = Me_3Si{\equiv}$, $R^2 = Me_3Si$; R^4 = H; **9, 2g, 4g**: R = Me_2CH, $R^1 = Me_3Si{\equiv}$, $R^2 = Me_3Si$, R_4 = H
10, 2h, 4h: R = Me, R^1 =  C_6H_5, $R^2 = Me_3Si$; R^4 = H; **11, 2i, 4i**: R = Me, $R^1 = CO_2Me$, $R^2 = R^4 = C_6H_4$-*p*-OMe;
12, 2l, 4l: R = Me, R^1 = 2-thienyl, $R^2 = Me_3Si$, R^4 = H; **11, 2m, 4m**: R = Me_2 CH, $R^1 = CO_2$ Me, $R^2 = R^4 = C_6H_4$-p-OMe

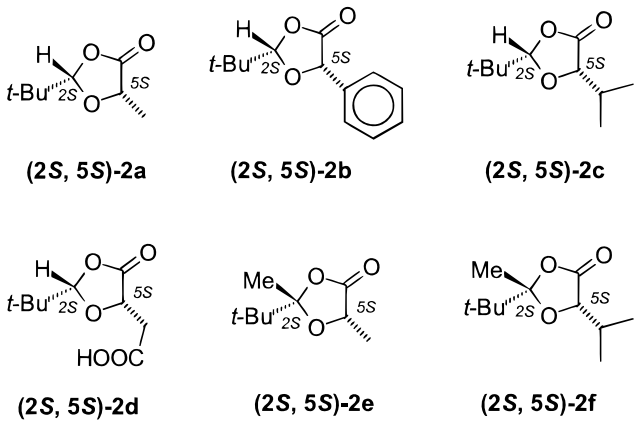


Figure 1. Dioxolanones **2a**−**f**.

used, as diastereomeric (2*S*,5*S*)cis/(2*R*,5*S*)-trans mixtures: **2a**[23a] (R = Me, 97:3), **2b**[23b] (R = C_6H_5, cis), **2c**[23b] (R = Me_2CH, 99:1), **2d**[23b] (R = CH_2CO_2H, 98:2). The (2*S*,5*S*)cis/(2*R*,5*S*)-trans mixtures of dioxolanones were converted into the corresponding nonracemic (2*S*)/(2*R*) mixtures of lithium enolates by reaction with lithium bis(trimethylsilyl)amide (LiHMDS). The 3-hydroxy-3-alkyl-β-lactams were obtained via cyclization of imines to the enolates (Scheme 1).

In a previous paper,[24] we reported a detailed study of the optimization of the addition reaction of the enolates **3a** and **3b** derived from lactones **2a** and **2b**, respectively, to imine **1**. According to this study, best results were obtained when the enolates were generated in situ by a slow addition of the lactones **2a** and **2b** to a mixture of LiHMDS and imine **1** at −95/−90 °C (**2a**) and at −50 °C (**2b**) in a THF/HMPA = 85:15 mixed solvent (procedure 1). The condensation of the enolates with imine **1**, the subsequent cyclization, and the elimination of the auxiliary center occurred in a one-pot sequence (Scheme 1) directly providing the β-lactams **4a** in a 69% yield (*Z*/*E* = 18:82)[25] and the β-lactams **4b** in an 82% yield (*Z*/*E* = 44:56).[26] Higher reaction temperatures were required when the imines were added to a THF solution of the enolates in the absence of HMPA. The yields of the β-lactams were greatly reduced.[27]

This procedure has now been extended to the reactions of imine **1** to the enolates **3c** and **3d** and to the reactions

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(25) An identical result was obtained when 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidone (DMPU), instead of HMPA, was used.

(26) In the previous communication,[24] an erroneous *Z*/*E* = 23:76 ratio, instead of 44:56, was given for the β-lactams **4b**.

(27) In the absence of HMPA, the β-lactams **4a** were obtained at −78/−50 °C as a *Z*/*E* = 64:36 mixture in 34% yields, 94% ee, while *Z*-**4b** was obtained at −5/+5 °C in 65% yield, 51% ee.[25] The formation of racemic *Z*-**4b** may be due to a competitive cycloaddition of imine **1** to the reactive phenylketene **6b** (Figure 4) that is formed from the decomposition of the enolate **3b**.

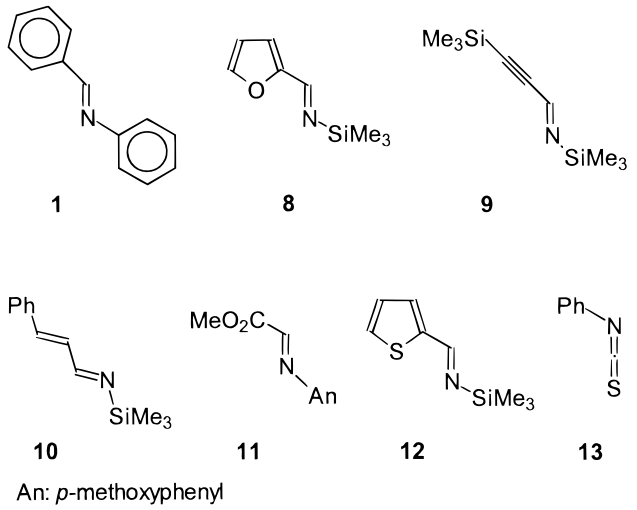


Figure 2. Azomethine components **1** and **8**−**13**.

Table 1. Product Distribution (yields, % ee) of *β*-Lactams 4a−i Obtained via Addition Reaction of Imines 1 and 8−11 to Enolates 3a−d (Procedure 1)

entry	imine	enolate **3** (*S*/*R*)	product	*3R,4S-Z*/*3R,4R-E* (yield (%), % ee)
1	**1**	**a** (97:3)	**4a**	18:82 (69, 94)[a]
2	**1**	**b** (*S*)	**4b**	44:56 (82, 99)[b]
3	**1**	c (99:1)	**4c**	71:29 (59, 97)[c]
4	**1**	**d** (98:2)	**4d**	78:22 (45, 99)[d]
5	**8**	**a** (97:3)	**4e**	66:33 (50, 96)[a]
6	**9**	**a** (97:3)	**4f**	33:66 (58, 98)[a]
7	**9**	**c** (99:1)	**4g**	18:82 (58, 96)[a]
8	**10**	**a** (97:3)	**4h**	95:5 (41, 98)[a]
9	**11**	**a** (97:3)	**4i**	50:50 (24, 94)[a]

Expected % ee: [a]94. [b] 100. [c] 98. [d] 96.

of enolate **3a** with other variants of the azomethine component, i.e. the *N*-(trimethylsilyl)-2-furylimine (**8**), bis-(trimethylsilyl)-propargylimine (**9**), *N*-(trimethylsilyl)-cinnamylideneimine (**10**), *N*-*p*-methoxyphenylimino-methylglyoxylate (**11**), and the azacumulene phenylisothiocyanate (**13**) (Figure 2 and Scheme 1). The use of the *N*-trimethylsilyl and *N*-*p*-methoxyphenyl substituents in aldimines is particularly attractive for the creation of monocyclic N-unsubstituted (*3R,4S*)-3-hydroxy-3-alkyl-*β*-lactams, which are useful substrates for the "*β*-lactam synthon method".[3] In addition, the aromatic isothiocyanates, such as the phenylisothiocyanate **13**, are used to prepare thiono-malonamic esters[28] from which 4-thiono-*β*-lactams are obtained. Yields, product distribution, and enantiomeric excesses (% ee) of the *β*-lactams **4a**−**i** derived from the reactions of imines **1** and **8**−**11** with enolates **3a**−**d** are collected in Table 1. The assignment of stereostructures was based on X-ray analyses, on chemical correlation, and on a combined NMR and circular dichroism spectroscopic study. The *E*/*Z* relative configuration of the *β*-lactams **4a**, **4c**, **4d**, and **4e** was established by a study of their ^{1}H NMR spectra. The methyl protons of *E*-**4a** and *E*-**4e**, the proton resonance of the Me_2CH group of *E*-**4c**, and the methylene protons of *E*-**4d** are in the shielding cone of the aromatic C4-phenyl and C4-furyl substituents. Their signals are, therefore, more upfield than the corresponding signals

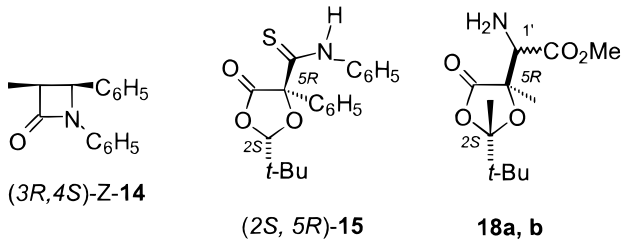


Figure 3. Compounds (*3R,4S*)-*Z*-**14**, (*2S,5R*)-**15**, and **18a** and **b**.

of the *Z*-diastereomers which have the hydroxy group in the shielding cone of the aromatic substituents. Qualitative homonuclear NOE difference spectra performed on the *β*-lactams **4a** and **4c**−**i** further confirmed these assignments.[29] The *E*/*Z* relative configuration of the *β*-lactams **4b** was assigned by a comparison of their physical and spectroscopic characteristics with those reported for the racemic forms.[5a,30] A chemical correlation of the absolute configuration (*3R,4R*) of the *β*-lactam *E*-**4a** with the *β*-lactam 1,4-diphenyl-3-methylazetidinone (*3S,-4S*)-*Z*-**14** (Figure 3) has already been described.[24] Additional studies regarding the assignment of the relative *E*-configuration of the *β*-lactam **4a** and of the absolute configuration of (*3R,4S*)-*Z*-**4b** by X-ray analysis together with the assignment of the absolute configuration of the other *β*-lactams from a comparison of their CD spectra with those of (*3R,4R*)-*E*-**4a** and (*3R,4R*)-*E*-**4b** are reported in a separate paper.[31] Only in one case (Table 1, entry 9, compound **4i**), the yield was exceptionally low (24%) because of the instability of the glyoxylic imine **11** under the basic reaction conditions. In the other cases, the yields ranged between moderate (41%, compound **4h**) and high (82%, compound **4b**). Major limitations are the steric demand of the substituents in the reagents and the instability of the cyclic enolates when long reaction times are required. For this reason, both the presence of the highly polar cosolvent HMPA and a slow addition of the dioxolanone into a mixture of imine and LiHMDS is necessary for an efficient conversion of the reagents into *β*-lactams. The polarity of the mixed solvent increases the reactivity of the substrates at low temperatures substantially reducing the formation of self-addition products, such as **5**, the decomposition of enolates **3** leading to the ketenes **6**,[32] and the formation of lactone alcohols **7** (Figure 4). The reaction of enolate **3a** and bis-(trimethylsilyl)-propargylimine (**9**) gave a mixture of 3-hydroxy- and 3-trimethylsilyloxy-*β*-lactams (**4f** and **4f′**) (Figure 5).[33] Similarly, the enolate **3c** and the imine **9** gave a mixture of *β*-lactams **4g** and **4g′**.[34] The yields reported in entries 6 and 7 of Table 1 refer to the total

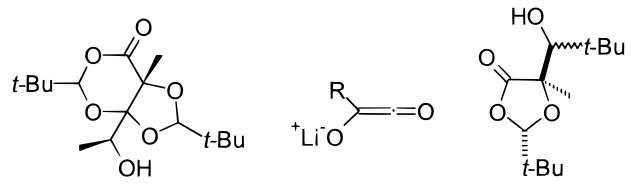
(28) Cainelli, G.; Giacomini, D.; Panunzio, M.; Martelli, G.; Spunta, G. *Tetrahedron Lett.* **1987**, *28*, 3593−3596 and references therein.

(29) In particular, the irradiation of the signals of the *Z*-diastereomers centered at 1.10 (C3−*Me* of **4a**), 2.25 (CH of C3−C*H*Me$_2$ of **4c**), 3.09 (CH$_2$ of C3−C*H*$_2$CO$_2$H of **4d**), 1.64 (C3−*Me* of **4e**), 1.56 (C3−*Me* of **4f**), 2.05 (CH of C3−C*H*Me$_2$ of **4g**), 1.50 (C3−*Me* of **4h**), 1.71 (C3−*Me* of **4i**), 1.63 (C3−*Me* of **4l**), and 2.20 (CH of C3−C*H*Me$_2$ of **4m**) showed a large enhancement (8.5−11%) of the neighboring C4−H protons centered at 5.10 (**4a**), 5.07 (**4c**), 5.52 (**4d**), 4.62 (**4e**), 4.17 (**4f**), 4.18 (**4g**), 4.17 (**4h**), 4.45 (**4i**), 4.83 (**4l**), and 4.48 (**4m**), respectively, while the corresponding *E*-isomers showed enhancements in the range of 1−3%.

(30) (a) Cossio, F. P.; Palomo, C. *Tetrahedron Lett.* **1985**, *35*, 4239−4242. (b) Bose, A. K.; Dayal, B.; Manhas, M. S.; Kapur, J. C.; Lal, B. *Tetrahedron Lett.* **1974**, *36*, 3135−3138.

(31) Barbaro, G.; Battaglia, A.; Guerrini, A.; Bertucci, C.; Geremia, S. *Tetrahedron Asymm.* **1998**, *9*, 3401−3409.

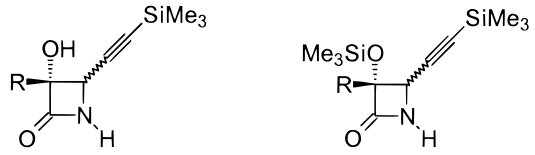
(32) See also: (a) Ogawa, T.; Niwa, H.; Yamada, K. *Tetrahedron* **1993**, *49*, 1571−1578. (b) Reference 23b.



5a **6a-c** **7a, 7c, 7d**

a: R = Me; **b**: R = C_6H_5; **c**: R = Me_2CH, **d**: R = CH_2CO_2H

Figure 4. Byproducts **5a**, **6a**−**c**, **7a**, **7c**, and **7d**.



4f, 4g **4f', 4g'**

4f, 4f': R = Me; **4g, 4g'**: R = Me_2CH

Figure 5. Compounds **4f**, **4f′**, **4g**, and **4g′**.

amount of β-lactams **4f** and **4g** obtained after a selective O-desilylation of **4f′** and **4g′** with a 3.0 M solution of acetic acid in methanol at 60 °C.[35] The reaction of phenylisothiocyanate **13** with **3b** gave the thiono-malonamic ester *(2S,5R)*-**15** in 75% yield (Figure 3). It is worth noting that these C4 substituents are also designed for the synthesis of modified bicyclic penems via a step-by-step synthesis of key cyclization precursors.[36]

All the reactions occurred with excellent face-selectivity. Enantioselective HPLC analysis (see Experimental Section) showed that both diastereoisomers (*3R,4S*)-*Z* and (*3R,4R*)-*E* of **4a** were obtained as enantiomer couples in a 97:3 ratio, 94% ee. This result indicated that the cycloaddition occurred under total facial-diastereocontrol since the obtained 94% ee corresponds to that expected on the basis of the diastereomeric excess (de) of the starting lactone. Similar results were obtained for the other β-lactams (Table 1). The assignment of the *3R* absolute configuration at the stereogenic C3 quaternary center of the major (*3R,4S*)-*Z*- and (*3R,4R*)-*E*-β-lactams is in agreement with the mechanism proposed by Seebach for the addition of electrophiles to the enolates having (*2S*)-chirality. The electrophilic imine approaches the enolate from the face opposite the *tert*-butyl substituent (Scheme 1). In particular, the diastereoisomeric (*3R,4S*)-*Z*-β-lactams are formed when the enolates having (*2S*)-chirality and **1** approach with a relative *lk,ul*-1,3 topicity, while (*3R,4R*)-*E*-diastereoisomers are derived from a relative *ul,ul*-1,3 topicity. Although the cyclic enolates possess a clean *Z*-geometry, the β-lactams were obtained with variable diastereoselectivity, this being the result of steric and electronic effects caused by the removal of the lithium ion by HMPA.[37] In addition, it has been shown[5b] that *N*-aryl-C3,C4-disubstituted-β-lactams easily isomerize in the presence of HMPA under the basic reaction conditions. This possibility cannot be excluded in our reactions. Control experiments demonstrated that *E*- and *Z*-**4a** and *E*- and *Z*-**4b** resist isomerization upon treatment with 0.2 equiv of LHMDS at 0 °C for 6 h in a THF/HMPA = 85:15 mixed solvent.[38] By contrast, a 1:1 *Z*/*E* mixture of **4i** was converted into a 1:2 mixture when this experiment was conducted at − 40 °C in 3 h. *E*-Diastereomers were preferentially formed in the reactions of diphenylimine **1** with the enolates **3a** and **3b** and in the reactions of propargylimine **9** with **3a** and **3c**. In the other cases, the *Z*-diastereomers were favored. Chromatography allowed the isolation of pure *E*- and *Z*-β-lactams **4a**−**c**, and **4f** and of the major isomers (*3R,4S*)-*Z*-**4d**, (*3R,4S*)-*Z*-**4e**, (*3R,4R*)-*E*-**4g**, and (*3R,4S*)-*Z*-**4h**, while the minor isomers (*3R,4R*)-*E*-**4d**, (*3R,4R*)-*E*-**4e**, (*3R,4S*)-*Z*-**4g**, and (*3R,4R*)-*E*-**4h** were isolated as variable diastereomeric mixtures. The chromatography of the β-lactams **4i** allowed their purification but failed in separating the product mixtures.

Reactions of Imines and Dioxolanones Derived from Pinacolone. The reactions so far described give excellent *3R* stereocontrol but diastereoselectivity is generally poor (de ≤ 64). Diastereoselectivity is particularly essential when the N-unsubstituted 3-hydroxy-3-methyl-β-lactams, with proper (*3R,4S*) stereochemistry, are used as intermediates in the synthesis of taxoids.[20] To improve the stereocontrol and at the same time avoid competition between the formation of β-lactams and side-products, such as **5** and **7**, we investigated the reactivity of two dioxolanones derived from pinacolone as the acetalization reagent, namely, dioxolanone **2e** [(*2S,5S*)-cis/(*2R,5S*)-trans = 96:4],[39] with a small Me substituent at C5 and the homochiral dioxolanone (*2S,5S*)*cis*-**2f** with a larger Me_2CH (Figure 1). Since the enolates derived from pinacolone are more stable than the corresponding enolates derived from pivalaldehyde, we used a different protocol for this study (procedure 2). The imine was added after the enolate was generated with LiHMDS in a 85:15 THF/HMPA mixed solvent. In Table 2, the product distribution, yields, and ee of the reactions of **2e** with imines **1** and **8**−**12** and of **2f** with **11** are reported. Similarly to enolate **3a**, all the reactions involving enolate **3e** occurred with excellent facial selectivity. We observed remarkable differences in the yields and stereochemical output when the results of the reactions of the enolates **3a** and **3e** with the same imines are compared. In several cases, the substitution of the small proton substituent at C2 of **3a** with a larger methyl of **3e** increased the yields and the diastereoselectivity favoring the major diastereomer. Quite interestingly, the β-lactam **4i**, derived from the glyoxylimine **11** and enolate **3e**, was obtained in good

(33) Relevant ^{1}H NMR spectroscopic characteristics of β-lactams **4f′**. ***(3R,4R)-E*-4f′**: ^{1}H NMR ($CDCl_3$) δ 0.17 (s, 9H), 0.18 (s, 9H), 1.53 (s, 3H), 4.10 (s, 1H), 6.25−6.35 (br s, 1H). ***(3R,4S)-Z*-4f′**: ^{1}H NMR ($CDCl_3$) δ 0.17 (s, 9H), 0.22 (s, 9H), 1.54 (s, 3H), 4. 07 (s, 1H), 6.40−6.50 (br s, 1H).

(34) Relevant ^{1}H NMR spectroscopic characteristics of β-lactams **4g′**. ***(3R,4R)-E*-4g′**: ^{1}H NMR ($CDCl_3$) δ 0.17 (s, 9H), δ 0.21 (s, 9H), 1.06 (d, 3H) 1.10 (d, 3H), 2.22 (m, 1H), 4. 05 (s, 1H), 5.90−6.00 (br s, 1H). ***(3R,4R)-Z*-4g′**: ^{1}H NMR ($CDCl_3$): δ 0.18 (s, 9H), 0.95 (d, 3H) 1.01 (d, 3H), 1.90 (m, 1H), 4. 10 (s, 1H), 6.25−6.35 (br s, 1H).

(35) The *E*/*Z* diastereomeric ratios of **4f** and **4f′** and of **4g** and **4g′** were identical.

(36) The conversion of the monocyclic β-lactams into bicyclic β-lactams should involve the conversion of the methoxycarbonyl, 2-furyl, propargyl, and phenylethenyl substituents into the corresponding 4-acetoxy- or the 4-(hydroxymethyl)-derivatives. See for example: Georg, G. I.; Kant, J.; Gill, H. S. *J. Am. Chem. Soc.* **1987**, *109*, 1129−1135 and references therein.

(37) It is worth noting that the relative amount of the chelation-controlled β-lactams **Z-4a** and **Z-4b** increased when the reactions of entries 1 and 2 (Table 1) were performed in the absence of HMPA. See refs 24 and 27.

(38) However, pure ***E*-4b** converted into a *E*/*Z* = 4:1 mixture upon treatment with an equimolar amount of NaH in THF under reflux for 1 h.

(39) Ortholand, Y. J.; Greiner, A. *Bull. Soc. Chim. Fr.* **1993**, *130*, 133−142.

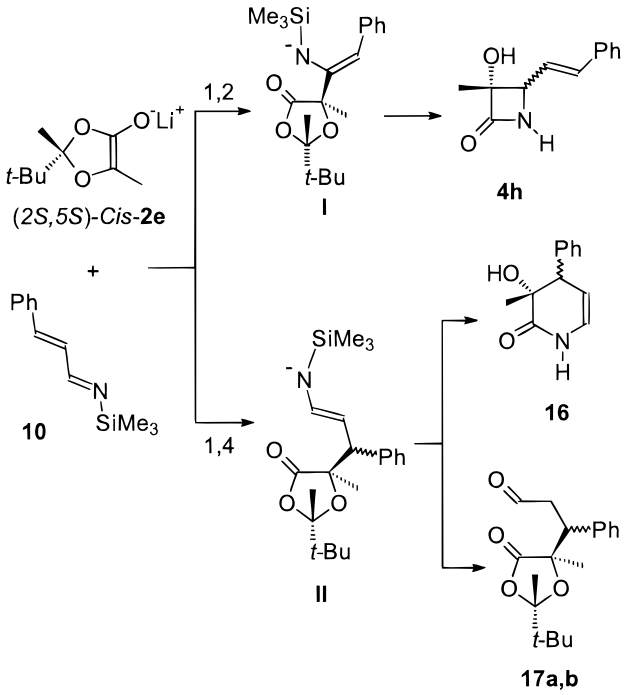
Table 2. Formation of β-Lactams 4a, 4e, 4f, and 4h−m via Addition Reaction of Imines 1 and 8−12 to the Enolates 3e and 3f (Procedure 2)

entry	imine	enolate **3** (*S*/*R*)	product	*3R,4S-Z*/*3R,4R-E* (yield %, % ee)
1	**1**	**e** (96:4)	**4a**	8:92 (87,92)[a]
2	**8**	**e** (96:4)	**4e**	80:20 (78, 92)[a]
3	**9**	**e** (96:4)	**4f**	5:95 (74, 98)[a]
4	**10**	**e** (96:4)	**4h**	92:8 (44, 98)[a]
5	**11**	**e** (96:4)	**4i**	84:16 (71, 92)[a]
6	**12**	**e** (96:4)	**4l**	94:6 (77, 92)[a]
7	**11**	**f** (*S*)	**4m**	92:8 (45, 62)[b]

Expected % ee: [a]92. [b] 100.

yields (71%). This was probably due to the inversion of the addition order of the reagents so that the decomposition of the unstable imine under the basic reaction conditions was substantially reduced. The major isomer (*3R,4S*)-*Z*-**4i** was isolated by chromatography or by crystallization. However, the product distribution of **4i** was dependent on the reaction conditions. Namely, total enantiofacial selectivity and good *Z*/*E* diastereoselectivity (84:16) were obtained when the reaction was performed at −105 °C. However, the *Z*/*E* ratio and the enantioselectivity decreased when the reaction was carried out at higher temperatures. Independent experiments showed that both a *Z* to *E* epimerization and racemization occurred when pure *Z*-**4i** was left to stand at higher temperatures (−60 °C) under the basic reaction conditions. The formation of amounts of byproducts was unavoidable in some reactions. In particular, the reaction of enolate **3e**, similarly to **3a**, gave a mixture of 3-hydroxy- (**4f**, 74%) and 3-trimethylsilyloxy-β-lactams (**4f′**, 9%). The reaction of **2e** and *N*-(trimethylsilyl)-cinnamylideneimine (**10**) gave the expected β-lactams **4h** and byproducts deriving from the 1,4-addition of the imine to the enolate, namely, the δ-lactam **16** (5%) and the dioxolanone derivatives **17a**, and **b** (18%). The result can be understood considering this possible reaction mechanism (Scheme 2). A competitive addition of the enolate anion to both the electrophilic carbon atoms of the imine (C1 and C3) leads to two acyclic aminoester intermediates **I** and **II**, which evolve into the corresponding four- or six-membered cyclic structures **4h** and **16**[40] or to the open chain 1,4-addition products **17**.[41,42] Finally, the reaction

Scheme 2. Proposed Mechanism for the Addition Reaction between Dioxolanone 2e and *N*-(Trimethylsilyl)-cinnamylideneimine (10)



of imine **11** and **2e** gave the expected β-lactams **4i** and a 1:1 mixture of the lactone derivatives **18a** and **18b** (20%)[43] (Figure 3). Similarly to the results obtained with enolate (*2S*)-**3e**, the high diastereoselectivity (*Z*/*E* = 92:8) for β-lactam **4m** is probably due to the bulkiness of the Me_2CH substituent of the homochiral enolate (*2S*)-**3f**, even if poor face-selectivity (62% ee) is observed.

Conclusions. Overall, this methodology appears to be a rather direct approach to chiral 3-hydroxy-β-lactams with full control of stereochemistry at the quaternary C3 carbon atom and a variety of substituents at C3 and C4, which are easily available from the inexpensive starting reagents. The diastereoselectivity is relatively low when β-lactams are prepared from enolates **3a**−**d** but significantly increases when the enolate **3e** is used. This allows an easy purification of the major diastereomer by a simple crystallization procedure. It is worth noting that four N-unsubstituted 3-hydroxy-3-methyl-β-lactams bearing 2-furyl (**4e**), 2-thienyl (**4l**), phenylethenyl (**4h**), and carbomethoxy (**4i**) substituents at C4, with proper (*3R,4S*) stereochemistry, were obtained in good yields, with high diastereomeric excesses, and were easily purified by column chromatography or by crystallization. The simultaneous presence of these substituents at C3 and C4 open the possibility of the synthesis of analogues of the antitumor drugs Taxol (paclitaxel) and Taxotère (docetaxel) using a protocol independently developed by Ojima and by Holton.[44]

(40) Relevant spectroscopic data of **(*3S*)-3-hydroxy-3-methyl-4-phenyl-3,4-dihydro-1H-pyridin-2-one (16)**: ^{1}H NMR (CD_3COCD_3) δ 0.99 (s, 3H), 3.90 (t, *J* = 2.8 Hz, 1H), 4.2 (br s, 1H), 5.2 (m, *J* = 7.8 Hz, 1H), 6.35 (m, *J* = 7.8 Hz, 1H), 7.2−7.5 (m, 5H), 8.4−8.7 (br s, 1H); ^{13}C NMR (DMSO/$CDCl_3$) δ 18.9, 48.6, 70.4, 107.5, 124.0, 125.4, 126.3, 128.2, 137.5, 173.1; MS *m*/*z* 203 (M^+), 160, 132, 115.

(41) Relevant spectroscopic data of **(*2S,5R,1′S* and *2S,5R,1′R*)-2-*t*-butyl-2,5-dimethyl-5-(3′-oxo-1′-phenylpropyl)-1,3-dioxolan-4-ones (17a and 17b)**: MS *m*/*z* 304 (M^+), 205, 172, 159; ^{1}H NMR (CD_3COCD_3) δ 0.95 (s, 9 H, 3Me of **17a**), 0.99 (s, 9H, 3Me of **17b**), 1.32 (s, 3H, Me of **17b**), 1.33 (s, 3H, Me of **17a**), 1.42 (s, 3H, Me of **17b**), 1.57 (s, 3H, Me of **17a**), 2.92−3.20 (m, 2H, CH_2 of **17b**), 3.0−3.4 (m, 2H, CH_2 of **17a**), 3.68 (m, J_1 = 4.2 Hz, J_2 = 9.5 Hz, 1H of **17b**), 3.90 (m, J_1 = 5.4 Hz, J_2 = 8.9 Hz, 1H of **17a**), 7.2−7.4 (m, 5H of **17a** and **17b**), 9.59 (m, 1H, C*H*=O of **17b**), 9.65 (m, 1H, C*H*=O of **17a**); ^{13}C NMR ($CDCl_3$) relevant data: δ 20.3 (Me of **17a**), 21.8 (Me of **17b**), 22.0 (Me of **17b**), 23.0 (Me of **17a**), 24.8 (3 Me of Me_3C of **17a**), 25.07 (3 Me of Me_3C of **17b**), 38.8 (C of **17a**), 38.9 (C of **17b**), 43.3 (CH_2 of **17a**), 45.1 (CH of **17a**), 45.2 (CH_2 of **17b**), 47.2 (CH of **17b**), 80.7 (C of **17a**), 81.6 (C of **17b**), 115.0 (C of **17b**), 115.1 (C of **17a**), 174.0 (C of **17b**), 174.9 (C of **17a**), 199.5 (C of **17a**), 199.7 (C of **17b**).

(42) The hypothesis that compounds **17** are derived by the reaction of **2e** with cinnamaldehyde, which may be formed by hydrolysis of imine **10**, was ruled out in an independent experiment. In fact, the reaction of cinnamaldehyde and the lithium enolate gave rise to corresponding dioxolanones derived by a 1,2-aldol addition, exclusively. An identical result has been observed in the reaction of cinnamaldehyde with **2a**.[23b]

(43) Relevant spectroscopic data of **(*2S,5R,1′S* and *2S,5R,1′R*)-2-*t*-butyl-2,5-dimethyl-5-[1′-(4-methoxyphenylamino)-1′-methoxycarbonyl-methyl]-1, 3-dioxolan-4-ones (18a and 18b). 18a**: ^{1}H NMR ($CDCl_3$) δ 1.1 (s, 9H), 1.58 (s, 3H), 1.71 (s, 3H), 3.70 (s, 3H), 3.71 (s, 3H), 4.10−4.20 (m, 2H), 6.70−6.80 (m, 4H); ^{13}C NMR ($CDCl_3$) relevant resonances δ 22.8, 23.0, 25.3, 38.8, 52.4, 55.7, 65.2, 81.7, 170.5, 173.1. **18b**: ^{1}H NMR ($CDCl_3$) δ 1.0 (s, 9H), 1.61 (s, 3H), 1.67 (s, 3H), 3.70 (s, 3H), 3.73 (s, 3H), 4.10−4.20 (m, 2H) 6.75 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 22.2, 22.7, 24.4, 25.2, 39.0, 52.4, 55.7, 65.5, 82.5, 114.8, 116.1, 117.3, 171.1, 173.4.

Experimental Section

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 200 MHz spectrometer with Me_4Si or $CHCl_3$ (in $CDCl_3$) as internal standards. Mass spectra were recorded on a ion trap spectrometer with an ionization potential of 70 eV. Infrared spectra were recorded on a Fourier transform IR spectrometer. The HPLC system consisted of a Jasco PU 980 pump. UV and CD detection were obtained by a Jasco MD-910 multiwavelength detector and a Jasco J 710 spectropolarimeter. Chromatographic resolution was obtained with the following columns (Daicel, 25 × 0.46 cm i.d.): a Chiralpack AD (compounds **4a**−**c**, **4e**), a Chiralcel OJ (compounds **4d**, **4f**, **4g**, **4h**, and **4l**), and a Chiralcel OD (compounds **4h**, **4m**). The mobile phase was *n*-hexane/2-propanol/acetic acid (75:25:1.5) in the case of **4d**, while mixtures of *n*-hexane/2-propanol (90:10−97.5:2.5) were used in all the other cases. The flow was 0.8−1.0 mL/min. The dioxolanones were prepared according to the literature and were purified by distillation under a vacuum. The enantiomeric excesses (ee) of the corresponding enolates are given in Tables 1 and 2. In particular, (*2S*,*5S*)-*cis*-**2f** was prepared for the first time according to literature procedure.[39] *N*-Trimethylsilylimines **8**, **9**, **10**, and **12** were prepared according to literature procedures.[45]

(*2S*,*5S*)-*cis*-2-*tert*-Butyl-2-methyl-5-isopropyl-1,3-dioxolan-4-one [(*2S*,*5S*)-*cis*-2f]: bp 83−84 °C/14 mmHg; IR ν_{max} ($CDCl_3$) 1798 (C=O) cm^{-1}; MS *m*/*z* 200 (M^+), 144; $[\alpha]^{22}_D$ = +10.0 (c 2.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.12 (d, 1H), 2.12 (m, *J* = 7.4 Hz, 1H), 1.44 (s, 3H) 1.10 (d, 3H), 1.01 (s, 9H), 1.00 (d, 3H); ^{13}C NMR ($CDCl_3$) δ 17.6, 18.1, 18.6, 24.3, 29.8 37.8, 77.7, 114.2, 172.5. Anal. Calcd for $C_{11}H_{20}O_3$: C 65.97, H 10.07. Found: C 65.80, H 10.11.

General Procedure for the Synthesis of the β-Lactams. The β-lactams were prepared according to the following procedures.

Procedure 1. A THF solution of dioxolanone was added via a syringe pump (5−7 h) to a THF/HMPA (85:15) solution of imine and LHMDS at the selected reaction temperature under stirring. Occasionally, the temperature was raised for the time required. Unless otherwise stated, the reaction mixture was treated with a saturated aqueous solution of NH_4Cl. The organic layer was extracted two times with brine and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The *E*/*Z* isomer distribution was evaluated from ^{1}H NMR analysis of the residue. The *E*/*Z*-mixture of diastereomeric β-lactams was separated by flash-chromatography or, when possible, by crystallization. When procedure 1 was used, the *N*-trimethylsilylimines **8**, **9**, and **12** were prepared in situ.[45] A THF solution of aldehyde (1.0 equiv) was added at −10 °C to a 1 M THF solution of LHMDS (1.2 equiv). The resulting solution was stirred for 20 min at 0 °C, then 1.0 equiv of trimethylchlorosilane was added. After the resulting solution was cooled to − 90 °C, a 1 M THF solution of LHMDS (0.63−0.70 equiv) and HMPA (THF/HMPA, 85:15) were sequentially added. Finally, a THF solution of dioxolanone (0.63−0.70 equiv) was added at the selected reaction temperature.

Procedure 2. A THF solution of the lactone was added to a THF solution of lithium diisopropylamide at − 78 °C. After 30 min, solutions of HMPA and imine were sequentially added at the selected temperature (THF/HMPA = 85:15). Unless otherwise stated, the reaction mixture was treated as described in procedure 1. Overall yields, *E*/*Z* isomer distribution, and ee of the β-lactams (together with their expected ee) are given in Tables 1 and 2. The synthesis and analytical data of *E*/*Z*-β-lactams **1a** and **1b** from dioxolanone **2a** have already been reported.[24]

Reaction of Imine 1 and Dioxolanone 2e. A THF solution of imine **1** (3.29 mmol) was added to a THF/HMPA solution of the enolate **3c** (2.03 mmol,) at −90 °C in 2 h. The temperature was raised to −70 °C for 2 h. Chromatography (SiO_2, EtOAc/*n*-pentane, 2:13) gave 1.76 mmol (87%, *Z*/*E* = 8:92) of β-lactams **4a**.

E*- and *Z*-3-Hydroxy-3-isopropyl-4-phenyl-*N*-4-phenylazetidin-2-ones [(*3R*,*4R*)-*E*-4c and (*3R*,*4S*)-*Z*-4c].** The dioxolanone **2c** (1.61 mmol) was added to a THF/HMPA solution of the imine **1** (3.00 mmol) and LHMDS (2.9 mmol) at − 90 °C in 8 h. Chromatography (SiO_2, EtOAc/*n*-pentane, 2:13) gave 0.95 mmol (59%, *Z*/*E* = 71:29) of β-lactams: IR ν_{max} ($CDCl_3$) 3650, 3550−3100, 1755 (N−C=O) cm^{-1}; MS *m*/*z* 282 (M^+ + 1), 264, 182, 133. **(*3R*,*4R*)-*E: mp 149−150 °C; $[\alpha]^{22}_D$ = −64 (c 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.47 (d, *J* = 6.6 Hz, 3H), 1.15 (d, *J* = 6.6 Hz, 3H), 2.05 (m, 1H), 2.80−2.90 (br s, 1H), 5.00 (s, 1H), 7.00−7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.7, 16.9, 29.3, 70.0, 90.5, 118.0, 124.2, 127.7, 128.6, 128.7, 129.0, 134.3, 137.1, 168.3. Anal. Calcd for $C_{18}H_{19}NO_2$: C 76.84, H 6.81, N 4.98. Found: C 76.60, H 6.86, N 5.02. **(*3R*,*4S*)-*Z***: mp 173−174 °C; $[\alpha]^{22}_D$ = + 180 (c 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.13 (d, *J* = 6.9 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 3H), 2.25 (m, 1H), 2.30−2.70 (br s, 1H), 5.07 (s, 1H), 7.00−7.45 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 16.7, 17.0, 33.2, 65.2, 89.1, 117.6, 124.3, 127.2, 128.8, 129.1, 129.3, 134.0, 137.1, 168.0.

E*- and *Z*-3-Carboxymethyl-3-hydroxy-4-phenyl-*N*-phenylazetidin-2-ones [(*3R*,*4R*)-*E*-4d and (*3R*,*4S*)-*Z*-4d].** A THF solution of dioxolanone **2d** (0.12 mmol) was added at −80 °C in 8 h to a THF/HMPA solution of **1** (0.22 mmol) and LHMDS (1 M in THF, 3.4 mL). The temperature was raised to −20 °C in 2 h. HCl (1 M, 10 mL) was added to the reaction mixture and extracted with ethyl acetate/CH_2Cl_2 = 3:1. The organic layer was treated with 50 mL of saturated aqueous $NaHCO_3$. The aqueous solution was extracted with ethyl acetate and then with CH_2Cl_2 and acidified with 1 M HCl. The mixture was extracted with ethyl acetate and then with CH_2Cl_2. The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. Chromatography (SiO_2, CH_2Cl_2/MeOH, 9:1) gave 0.54 mmol (45%, *Z*/*E* = 78:22) of β-lactams **4d**. IR ν_{max} (THF) 3600−3100, 1755 (N−C=O), 1720 cm^{-1}; MS *m*/*z* 297 (M^+), 252, 251, 235, 181. **(*3R*,*4R*)-*E: ^{1}H NMR (CD_3COCD_3) δ 2.52 (q, *J* = 16.9 Hz, 2H), 3.60−3.90 (br s, 1H), 5.22 (s, 1H), 7.00−7.50 (m, 10H); ^{13}C NMR (CD_3COCD_3) δ 35.3, 69.9, 86.6, 118.5, 124.9, 129.0, 129.1, 129.8, 129.9, 135.2, 138.5, 166.8, 172.0. **(*3R*,*4S*)-*Z***: mp 146−148 °C; $[\alpha]^{22}_D$ = + 150 (c 0.5, THF); ^{1}H NMR (CD_3COCD_3) δ 3.09 (q, *J* = 16.0 Hz, 2H), 3.60−3.90 (br s, 1H), 5.52 (s, 1H), 7.00−7.50 (m, 10H); ^{13}C NMR (CD_3COCD_3) δ 39.8, 67.4, 84.4, 118.4, 124.7, 128.8, 129.0, 129.1, 129.8 135.6, 138.7, 167.4, 171.6. Anal. Calcd for $C_{17}H_{15}NO_4$: C 68.68, H 5.09, N 4.71. Found: C 68.88, H 5.13, N 4.77.

***E*- and *Z*-4-Furan-2-yl-3-hydroxy-3-methyl-azetidin-2-ones [(*3R*,*4R*)-*E*-4e and (*3R*,*4S*)-*Z*-4e]. (a) Reaction of *N*-Trimethylsilyl-2-furfuraldimine (8) and Dioxolanone 2a.** The imine **8** was prepared in situ from 2-furaldehyde (4.86 mmol), 5 mL of a 1 M solution of LHMDS, and 4.86 mmol of trimethylchlorosilane. A 1 M THF solution (3.06 mL) of LHMDS and HMPA were sequentially added. A THF solution of dioxolanone **2a** (2.21 mmol, *S*/*R* = 97:3) was added in 6 h at − 90 °C. The reaction mixture was left at −78 °C for 2 h and then at −50 °C for 2 h. The reaction was quenched with acetic acid, the solvent was evaporated under reduced pressure, and HMPA was distilled at 10^{-1} Torr. Chromatographic workup (SiO_2, EtOAc/CH_2Cl_2, 1:3) gave the β-lactams **4e** (1.10 mmol, 50%, *Z*/*E* = 2:1).

(b) Reaction of *N*-Trimethylsilyl-2-furfuraldimine (8) and Dioxolanone 2e. A THF solution of freshly distilled imine **8** (2.73 mmol) was added to a THF/HMPA solution of the enolate **3e** (1.70 mmol) at −78 °C. The reaction mixture was left at −90 °C for 2 h and then at −50 °C for 2 h. The chromatography gave 1.33 mmol (78%, *Z*/*E* = 80:20) of β-lactams **4e**: IR ν_{max} (THF) 3630, 3550−3100, 1770 (N−C=O) cm^{-1}; MS *m*/*z* 167 (M^+), 124, 110, 96. **(*3R*,*4S*)-*Z***: mp 127−

(44) According to this methodology, the phenylisoserine side-chains of paclitaxel and docetaxel are appended to the C13 of Baccatin IIIs with proper protecting groups via ring-opening coupling of (*3R*,*4S*)-1-acyl-3-silyloxy-4-phenyl-β-lactams with metalated baccatins. See for example: (a) Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C.-M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6895−7012. (b) Holton, R. A.; Biediger, R. J.; Boatman, P. D. In *Taxol: Science and Applications*; Suffness, M., Ed.; CRC: New York, 1995; pp 97−121.

(45) Colvin, E. W.; McGarry, D.; Nugent M. J. *Tetrahedron* **1988**, *44*, 4157−4172.

129 °C; $[\alpha]^{22}_D = +70$ (c 0.3, CH_3COCH_3); ^{1}H 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); ^{13}C NMR ($CDCl_3$) δ 20.1, 59.3, 86.2, 109.3, 110.7, 142.8, 150.3, 173.0. 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. ***(3R, 4R)-E***: ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 3 H), 2.90−3.00 (br s, 1H), 4.66 (s, 1H), 6.25−6.35 (m, 2H), 6.7−6.8 (br s, 1H), 7.40−7.45 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 18.0, 60.0, 87.4, 108.4, 110.5, 143.4, 150.4, 173.2.

***E*- and *Z*-3-Hydroxy-3-methyl-4-trimethylsilanylethynyl-azetidin-2-ones [(*3R,4R*)-*E*-4f and (*3R,4S*)-*Z*-4f]. (a) Reaction of Bis-trimethylsilylpropargylimine (9) and Dioxolanone 2a.** The imine **9** was prepared in situ from trimethylsilylpropargylaldehyde (4.86 mmol), 5 mL of a 1 M solution of LHMDS, and 4.86 mmol of trimethylchlorosilane. A THF solution of LHMDS (1 M, 3.06 mL) and HMPA were sequentially added. A THF solution of dioxolanone **2a** (1.66 mmol) was added in 4 h at −85 °C. The reaction temperature was raised to − 60 °C and left for 2 h. After the addition of a saturated aqueous solution of NH_4Cl, selective O-desilylation of the β-lactams **4f′** was performed by treating the reaction mixture with $MeOH/CH_3CO_2H$ (1:1) for 16 h at 25 °C. The solution was neutralized with a 2 N aqueous solution of $NaHCO_3$, extracted with CH_2Cl_2, and dried (Na_2SO_4). After evaporation of the solvent under reduced pressure, the residue was chromatographed (SiO_2, EtOAc/*n*-pentane, 1:4) to give the β-lactams **4f** (0.96 mmol, 58%, Z/E = 1:2).

(b) Reaction with Dioxolanone 2e. A THF solution of freshly distilled imine **8** (2.30 mmol) was added to a THF/HMPA solution of the enolate (1.70 mmol) at −90 °C. The reaction mixture was left at −90 °C for 2 h and then at −60 °C for 2 h. Workup of the reaction as described above gave 1.24 mmol (74%, Z/E = 5:95) of β-lactams **4f**: IR ν_{max} (THF) 3640, 3550−3100, 1765 (N−C=O) cm^{-1}; MS *m*/*z* 197 (M^+), 182, 157, 139, 126, 116, 109, 99, 75, 73. ***(3R,4R)-E***: mp 156−158 °C; $[\alpha]^{22}_D = +97$ (c 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.18 (s, 9H), 1.57 (s, 3H), 3.10−3.80 (br s, 1H), 4.22 (s, 1H), 6.10−6.20 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ −0.27, 19.3, 53.8, 86.9, 93.8, 100.0, 172.2. ***(3R,4S)-Z***: mp 134−136 °C; $[\alpha]^{22}_D = -50$ (c 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.19 (s, 9H), 1.56 (s, 3H), 3.40−3.50 (br s, 1H), 4.17 (s, 1H), 6.05−6.20 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ −0.31, 20.4, 53.7, 85.3, 95.4, 99.8, 171.4. Anal. Calcd for $C_9H_{15}NO_2Si$: C 54.79, H 7.66, N 7.10. Found: C 54.74, H 7.61, N 7.17.

E*- and *Z*-3-Hydroxy-3-isopropyl-4-trimethylsilanylethynyl-azetidin-2-ones [(*3R,4R*)-*E*-4g and (*3R,4S*)-*Z*-4g].** The imine **9** was prepared in situ from 4.5 mmol of LHMDS and 3.74 mmol of trimethylsilylpropargylaldehyde and 3.7 mmol of trimethylchlorosilane. Then, 3.06 mL of a 1 M THF solution of LHMDS and HMPA were sequentially added. A THF solution of dioxolanone (2.21 mmol) was added in 6 h at −85 °C. The reaction temperature was raised to −60 °C and left for 2 h. After the addition of a saturated aqueous solution of NH_4Cl, selective O-desilylation of the β-lactams **4g′** was performed by treating the reaction mixture with $MeOH/CH_3CO_2H$ (1:1) for 16 h at 25 °C. The solution was neutralized with a 2 N aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2. After evaporation of the solvent under reduced pressure, the residue was chromatographed (SiO_2, EtOAc/*n*-pentane, 1:4) to give the β-lactams **4g** (1.28 mmol, 58%, Z/E = 18:82): IR ν_{max} (THF) 3630, 3550−3100, 1760 (N−C=O) cm^{-1}; MS *m*/*z* 225 (M^+), 210, 182, 167, 144, 139, 126, 98, 75, 73. ***(3R,4R)-E: mp 119−121 °C; $[\alpha]^{22}_D = +140$ (c 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.17 (s, 9H), 1.12 (d, J = 6.9 Hz, 3H) 1.17 (d, J = 6.9 Hz, 3H), 2.34 (m, 1H), 3.0−3.30 (br s, 1H), 4.16 (s, 1H), 6.20−6.30 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ −0.5, 15.7, 16.4, 31.1, 53.2, 92.6, 93.7, 100.7, 171.4. Anal. Calcd for $C_{11}H_{19}NO_2Si$: C 58.63, H 8.50, N 6.21. Found: C 58.70, H 8.44, N 6.16. ***(3R,4S)-Z***: ^{1}H NMR ($CDCl_3$) δ 0.18 (s, 9 H), 1.01 (d, J = 6.8 Hz, 3H) 1.09 (d, J = 6.8 Hz, 3H), 2.05 (m, 1H), 3.10−3.25 (br s, 1H), 4.18 (s, 1H), 6.15−6.25 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ −0.1, 16.7, 17.14, 32.3, 50.6, 91.4, 95.6, 100.2, 171.0.

***E*- and *Z*-3-Hydroxy-3-methyl-4-(*E*)-styryl-azetidin-2-ones [(*3R,4R*)-*E*-4h and (*3R,4S*)-*Z*-4h]. (a) Reaction of *N*-Trimethylsilylcinnamaldimine (10) and Dioxolanone 2a.** A THF solution of dioxolanone **2a** (2.03 mmol) was added via a syringe pump (5 h) to a THF/HMPA solution of **10** (3.65 mmol) and LHMDS (3.65 mmol) at −85 °C in 5 h. The reaction mixture was left at − 50 °C for 3 h. The reaction mixture was treated at −50 °C with 4 mL of a 1 N aqueous solution of HCl and neutralized with a 2 N aqueous solution of $NaHCO_3$. The organic layer was extracted two times with brine and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and chromatography of the residue (SiO_2, EtOAc/*n*-pentane, 1:2) gave 0.83 mmol of **4h** (41%, Z/E = 95:5).

(b) Reaction of *N*-Trimethylsilylcinnamaldimine (10) and Dioxolanone 2e. The imine **10** (4.06 mmol) was added to a THF/HMPA solution of the enolate (2.03 mmol, S/R = 95:5) at −90 °C in 15 min. The reaction mixture was left at −90 °C for 60 min, then at − 70 °C for 3 h, and at −50 °C for 60 min. After the workup of the reaction mixture as described above, chromatography (SiO_2, EtOAc/*n*-pentane, 1:2) gave the β-lactams **4h** (1.78 mmol, 44%, Z/E = 92:8), compound **16** (0.10 mmol, 5%), and compounds **17** (0.23 mmol, 18%): IR ν_{max} ($CDCl_3$) 3650, 3550−3100, 1765 (N−C=O) cm^{-1}; MS (CI, CH_4) *m*/*z* 232 ($M^+ + 29$), 204 ($M^+ + 1$), 186. ***(3R,4R)-E***: ^{1}H NMR (CD_3COCD_3) relevant resonances at δ 1.29 (s, 3H), 4.25 (d, J = 8.0 Hz, 1H), 5.23 (br s, 1H). ***(3R,4S)-Z***: mp 158−160 °C; $[\alpha]^{22}_D = +1$ (c 0.5, $CHCl_3$); ^{1}H NMR (CD_3COCD_3) δ 1.50 (s, 3H), 2.70−2.80 (br s, 1H), 4.17 (d, J = 7.4 Hz, 1H), 4.95 (br s, 1H), 6.4 (dd, J_1 = 7.4 Hz, J_2 = 16.4 Hz, 1H), 6.7 (d, J = 16.4 Hz, 1H), 7.2−7.5 (m, 5H); ^{13}C NMR (CD_3COCD_3) δ 22.2, 64.2, 86.7, 127.3, 128.4, 129.4, 133.8, 137.8, 172.1. Anal. Calcd for $C_{12}H_{13}NO_2$: C 70.92, H 6.45, N 6.89. Found: C 70.80, H 6.48, N 6.95.

***E*- and *Z*-3-Hydroxy-4-methoxycarbonyl-3-methyl-*N*-4-methoxyphenyl-azetidin-2-ones [(*3R,4R*)-*E*-4i and (*3R,4S*)-*Z*-4i]. (a) Reaction of Imine 11 and Dioxolanone 2a.** The dioxolanone **2a** (2.03 mmol) was added to a THF/HMPA solution of the imine **11** (3.04 mmol) and LHMDS (3.0 mmol) at − 105 °C in 1 h. The reaction mixture was treated with 5 mL of a 1 M aqueous solution of CH_3CO_2H at −100 °C, with a 1 N aqueous solution of HCl, then with NH_4Cl, and then with brine. The organic phase was dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. Chromatography of the residue (SiO_2, EtOAc/*n*-pentane, 12:8) gave 0.46 mmol (20%) of a 1:1 mixture of β-lactams **4i**.

(b) Reaction of Imine 11 and Dioxolanone 2e. The imine **11** (3.04 mmol) was added to a THF/HMPA solution of the enolate **2e** (2.03 mmol) at −105 °C in 15 min. The reaction mixture was left at −100 °C for 2 h. Workup as described above gave the β-lactams **4i** (1.44 mmol, 71.0%, Z/E = 5.5:1) and a mixture of compounds **18a** and **18b** (0.34 mmol, 17%, **a**/**b** = 2.6): IR ν_{max} ($CHCl_3$) 3620, 3550−3100, 1710−1780 (N−C=O and CO_2Me) cm^{-1}; MS *m*/*z* 265 (M^+), 237, 194, 149, 134. ***(3R,4S)-Z***: mp 134−136 °C; $[\alpha]^{22}_D = +96$ (c 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.71 (s, 3H), 3.62 (br s, 1H), 3.78 (s, 3H), 3.84 (s, 3H), 4.45 (s, 1H), 6.80−7.30 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 21.2, 52.9, 55.5, 65.5, 84.3, 114.2, 118.4, 130.3, 156.8, 166.4, 169.3. Anal. Calcd for $C_{13}H_{15}NO_5$: C 58.86, H 5.70, N 5.28. Found: C 59.02, H 5.63, N 5.35. ***(3R,4R)-E***: ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 3H), 2.0−2.2 (br s, 1H), 3.77 (s, 3H), 3.83 (s, 3H), 4.52 (s, 1H), 6.80−7.30 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 17.8, 52.6, 55.5, 66.0, 85.2, 114.4, 118.8, 130.2, 156.9, 167.5, 168.6.

E*- and *Z*-3-Hydroxy-3-methyl-4-thien-2-yl-azetidin-2-ones [(*3R,4R*)-*E*-4l and (*3R,4S*)-*Z*-4l]. Reaction of *N*-Trimethylsilyl-2-thienylimine (12) and Dioxolanone 2e.** A THF solution of freshly distilled imine **12** (2.73 mmol) was added to a THF/HMPA solution of the enolate **3e** (1.70 mmol) at −78 °C. The reaction mixture was left at −78 °C for 2 h and then at −50 °C for 2 h. The reaction was quenched with acetic acid, the solvent evaporated under reduced pressure, and HMPA was distilled at 10^{-1} Torr. The chromatography gave 1.31 mmol (77%, Z/E = 94:6) of β-lactams **4l**: IR ν_{max} (THF) 3630, 3550−3100, 1770 (N−C=O) cm^{-1}; MS *m*/*z* 183 (M^+), 142, 112. ***(3R,4S)-Z: mp 133−134 °C; $[\alpha]^{22}_D = +70$ (c 0.8, CH_3COCH_3); ^{1}H NMR ($CDCl_3$) δ 1.63 (s, 3H), 3.20−3.30 (br s, 1H), 4.83 (s, 1H), 6.60−6.70 (br s, 1H), 7.00−7.50 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 21.2, 61.6, 86.0, 126.0, 126.1, 127.7, 139.9, 172.0. Anal. Calcd for $C_8H_9NO_2S$: C 52.44, H 4.95, N

7.64. Found: C 52.22, H 5.02, N 7.56. ***(3R,4R)-E***: ^{1}H NMR ($CDCl_3$) relevant resonances at δ 1.19 (s, 3H), 4.91 (s, 1H).

E*- and *Z*-3-Hydroxy-3-isopropyl-4-methoxycarbonyl-*N*-4-methoxyphenyl-azetidin-2-ones [(*3R,4R*)-*E*-4m and (*3R,4S*)-*Z*-4m].** The imine **11** (4.00 mmol) was added to a THF/HMPA solution of the enolate **2f** (2.03 mmol, S/R = 95:5) at −105 °C in 15 min. The reaction mixture was treated with 5 mL of a 1 M aqueous solution of CH_3CO_2H at − 100 °C, extracted with HCl (1 N), then with NH_4Cl, and then with brine. The organic phase was dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. Chromatography of the residue (SiO_2, EtOAc/*n*-pentane, 12:8) gave 0.90 mmol (45%, Z/E = 92:8) of β-lactams **4m**. IR ν_{max} ($CHCl_3$) 3620, 3550−3100, 1710−1780 (N−C=O and CO_2Me) cm^{-1}; MS *m*/*z* 293 (M^+), 194. ***(3R,4S)-Z: Oil; $[\alpha]^{22}_D$ = +65 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.07 (d, J = 6.9 Hz, 3H), 1.45 (d, J = 6.9 Hz, 3H), 2.20 (m, 1H), 3.78 (s, 3H), 3.83 (s, 3H), 4.48 (s, 1H), 6.80−7.30 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 16.4, 16.9, 32.9, 52.7, 55.4, 62.4, 90.3, 114.4, 118.3, 130.1, 156.7, 166.4, 169.3. Anal. Calcd for $C_{15}H_{19}NO_5$: C 61.42, H 6.53, N 4.78. Found: C 61.65, H 6.70, N 4.81. ***(3R,4R)-E***: ^{1}H NMR ($CDCl_3$) δ 0.93 (d, J = 6.8 Hz, 3H), 1.16 (d, J = 6.8 Hz, 3H), 2.28 (m, 1H), 3.74 (s, 3H), 3.78 (s, 3H), 4.43 (s, 1H), 6.80−7.30 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 15.9, 17.0, 29.8, 52.6, 55.5, 66.0, 91.2, 114.4, 118.6, 130.2, 156.9, 166.5, 169.0.

***(2S,5R)*-2-*t*-Butyl-5-(carbothioic acid)-5-phenyl-*N*-phenylamide-1,3-dioxolan-4-one *(2S,5R)*-15.** Phenylisothiocyanate (3.50 mmol) was added to a THF solution of the enolate (*S*)-**3b** (2.72 mmol) at −78 °C in 15 min. The reaction mixture was left at −78 °C for 3 h and then at −60 °C for 2 h. After quenching, compound **15** was purified by crystallization (0.72 g, 1.83 mmol, 75%): mp 109−111 °C; $[\alpha]^{22}_D$ = +130 (c 0.6, $CHCl_3$); IR ν_{max} ($CDCl_3$) 3600, 3500−3200, 1660, 1600, 1500, 1440, 1420, 1390 cm^{-1}; MS (CI, CH_4) *m*/*z* 384 (M^+ + 29), 356 (M^+ + 1), 314; ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 9H), 5.6 (s, 1H), 7.20−7.80 (m, 10H), 9.00−9.20 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.5, 34.6, 88.6, 109.4, 122.9, 126.1, 127.2, 128.9, 129.0, 129.6, 134.7, 137.9, 169.0, 192.4. Anal. Calcd for $C_{20}H_{21}NO_3S$: C 67.58, H, 5.96, N, 3.94. Found: C 67.69, H 5.90, N 3.98.

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