Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 2765–2773

TETRAHEDRON: *ASYMMETRY*

# New efficient synthesis of (3*R*,4*S*)-3-methyl-3-hydroxy-4-phenyl-β-lactam

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Received 11 June 1999; accepted 9 July 1999

**Abstract**

A method is described for the chiral synthesis of (3*R*,4*S*)-3-methyl-3-hydroxy-4-phenyl-β-lactam, a useful precursor for the semi-synthesis of 2′-methyl-taxoids. This protocol follows Seebach's synthetic principle of 'self-regeneration of stereocenters' (SRS) and has been applied to addition reactions of the (2*S*)-chiral enolates of dioxolan-4-ones, derived from the acetalization of (*S*)-α-lactic acid and *tert*-butylaldehyde or pinacolone, to *N*-trimethylsilylphenyl aldimine. 

## 1. Introduction

Taxol (paclitaxel) and its semi-synthetic derivative docetaxel (Taxotere) exhibit outstanding activity with various types of cancer.[1] In fact, paclitaxel inhibits cell replication in the mitotic phase of the cycle[2] by promoting polymerization of microtubules which are stable and resistant to depolymerization.[1d,f,3] Structure–activity relationship studies (SARs)[1,4] have shown that the phenylisoserine side-chain at position 13 of taxanes with proper 2′*R*,3′*S* configuration is essential. However, treatment with these drugs often results in various undesired side effects as well as multidrug resistance (MDR).[5] For this reason, a number of *N*,*O*-protected (2*R*,3*S*)-isoserine analogues have been synthesized[6] to be appended to C-13 of taxanes to improve MDR. Alternatively, (3*R*,4*S*)-1-acyl-3-hydroxy-4-phenyl-β-lactam derivatives bearing a suitable protecting substituent at the C-3 oxygen atom have also been designed,[7] and they have been directly appended to C-13 of taxanes via Holton's chemistry.[8] Kant[9] reported that taxoids, which bear an additional methyl substituent at the C-2 position of the phenylisoserine, display higher cytotoxic activity compared to the parents docetaxel and paclitaxel when evaluated in in vitro assays

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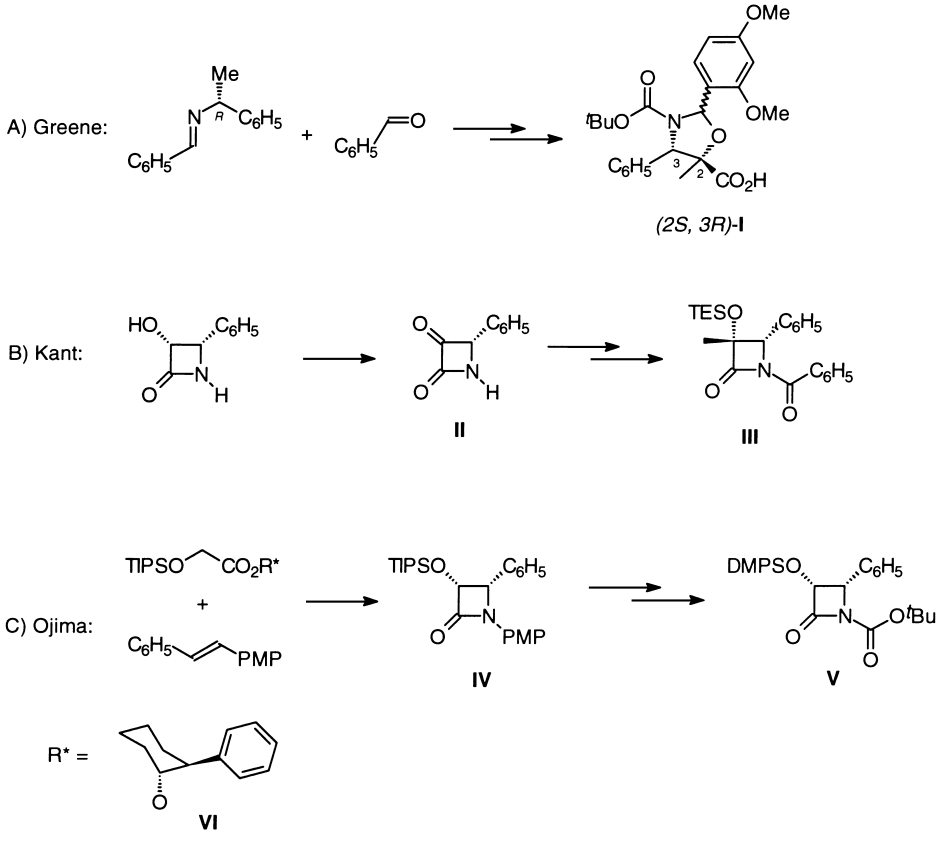
0957-4166/99/$ - see front matter 
*PII:* S0957-4166(99)00288-8

using HCT116 human colon carcinoma cell lines. The enhanced potency is probably the result of a reduction in the degree of freedom at the C2′–C3′ bond of the isoserine appendant or of some additional hydrophobic interactions between the methyl substituent and the microtubule binding sites. Greene,[10] Kant,[9] and Ojima[11] independently developed different approaches for the synthesis of synthons of the enantiopure C-2 methylated phenylisoserine. Greene synthesized, via a multistep process, the 2,4-dimethoxyphenyl-substituted oxazolidine free acid (2*S*,3*R*)-**I** (Scheme 1). Instead, Kant and Ojima independently synthesized enantiopure *O*-protected-1-acyl-3-methyl-β-lactam derivatives **III** and **V**. However, their synthesis requires non-readily available and expensive chiral inductors such as **VI**, and enantiopure β-lactam precursors such as **II** and **IV**. Moreover, both **III** and **V** are obtained in moderate to low (35–5%) yields via multi-step processes which require several deprotection–reprotection sequences. Recently, we have developed a new synthetic protocol for the asymmetric construction of trisubstituted 3-hydroxy-β-lactams in a versatile and predictable manner using easily available lithium enolates of acetal-type derivatives of (*S*)-α-hydroxy-substituted carboxylic acids and imines as starting reagents.[12] To achieve our target, we have applied the synthetic principle called 'self-regeneration of stereocenters' developed by Seebach[13] to the addition reactions of lithium enolates of the (2*S*,5*S*)-2-(*tert*-butyl)-5-methyl-1,3-dioxolan-4-one **1a** and (2*S*,5*S*)-2-(*tert*-butyl)-2,5-dimethyl-1,3-dioxolan-4-one **1b** (Fig. 1) to *N*-trimethylsilylphenyl aldimine.




PMP = *p*-methoxyphenyl; TES: triethylsilyl; TIPS = Triisopropylsilyl; DMPS = Dimethylphenylsilyl

Scheme 1.

## 2. Results and discussion

Diastereomeric (2*S*,5*S*)-*cis*:(2*R*,5*S*)-*trans* mixtures of **1a** (97:3)[14a] and **1b** (93:7)[14b] were prepared according to standard procedures. Even the single (1*S*,2*S*)-diastereomer of **1a** and **1b** can be easily obtained via recrystallization at low temperatures,[14b] for our study the *cis*:*trans* mixtures of dioxolanones were directly converted into the corresponding enolates (2*S*:2*R*)-**3a**=97:3 and (2*S*:2*R*)-**3b**=93:7 (Fig. 1) by reaction with lithium bis(trimethylsilyl)amide (LHMDS) or lithium diisopropylamide (LDA) in THF at low temperatures. The imine was prepared from benzaldehyde and LHMDS,[15] and reacted in situ or purified according to standard methodologies.[12c,15] Depending on the type of base used and on the structure of the enolate, different results were obtained.

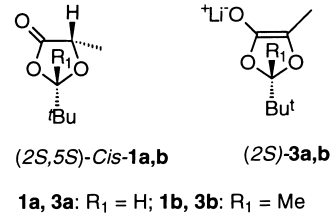
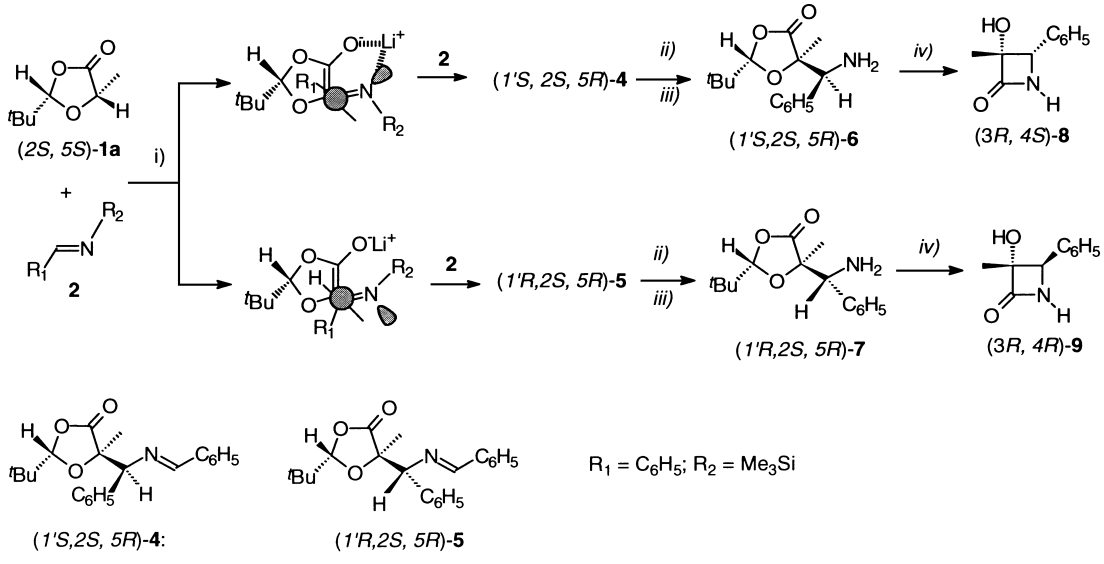



Figure 1. (2*S*,5*S*)-2-(*tert*-Butyl)-5-methyl-1,3-dioxolan-4-ones **1a** and **1b** and their lithium enolates (2*S*)-**3a** and (2*S*)-**3b**

### 2.1. Reaction of enolate (2S)-3a and imine 2

#### 2.1.1. Reaction with LHMDS

Best results were obtained when LHMDS, HMPA and a THF solution of dioxolanone **1a** were sequentially added at −90°C to an excess of aldimine **2** (THF:HMPA=85:15). The reaction gave an 8.8:1 mixture of imino-dioxolanone derivatives (1′*S*,2*S*,5*R*)-**4** and (1′*R*,2*S*,5*R*)-**5** (Scheme 2). The mixture of compounds **4** and **5** was directly hydrolyzed with 1N HCl at 20°C affording the amino-lactones (1′*S*,2*S*,5*R*)-**6** (37%) and (1′*R*,2*S*,5*R*)-**7** (4%).[16] MeMgBr-induced cyclization of amino-lactone **6** under Birkofer conditions[17] gave the β-lactam (3*R*,4*S*)-**8** in 68% yield.




Scheme 2. Synthesis of β-lactams **8** and **9**. Reagents and conditions: (*i*) LHMDS, THF:HMPA=85:15, −90°C, 4 h; (*ii*) HCl 1N, acetone:$H_2O$=1:1, 20°C, 6 h; (*iii*) $K_2CO_3$, 20°C, 1 h; (*iv*) MeMgBr, $Et_2O$, 25°C, 1 h

Chiral HPLC analysis showed that amino-lactones **6** and **7** were obtained in 94% enantiomeric excess (*ee*), corresponding to that expected on the basis of the diastereomeric excess (*de*) of the starting dioxolanone **1a**. This result indicated that the cycloaddition occurred under total facial diastereocontrol. The electrophilic imine approaches the enolate from the face opposite to the *tert*-butyl substituent (Scheme 2) in agreement with the mechanism proposed by Seebach for the addition of electrophiles to enolates having (2*S*)-chirality.[18] The relative 1′*S*,2*S*,5*R* stereoconfiguration of compound **6** was assessed by X-ray analysis whose ORTEP drawing is reported in Fig. 2. The sign (positive) of the circular dichroism band of (3*R*,4*S*)-**8** at 225 nm allowed the assessment of its absolute configuration.[12b] Moreover, the β-lactam (3*R*,4*S*)-**8** was chemically correlated with its ODMPS derivative (3*R*,4*S*)-**10** (Scheme 3) which has been synthesized by Ojima via a different route.[11]

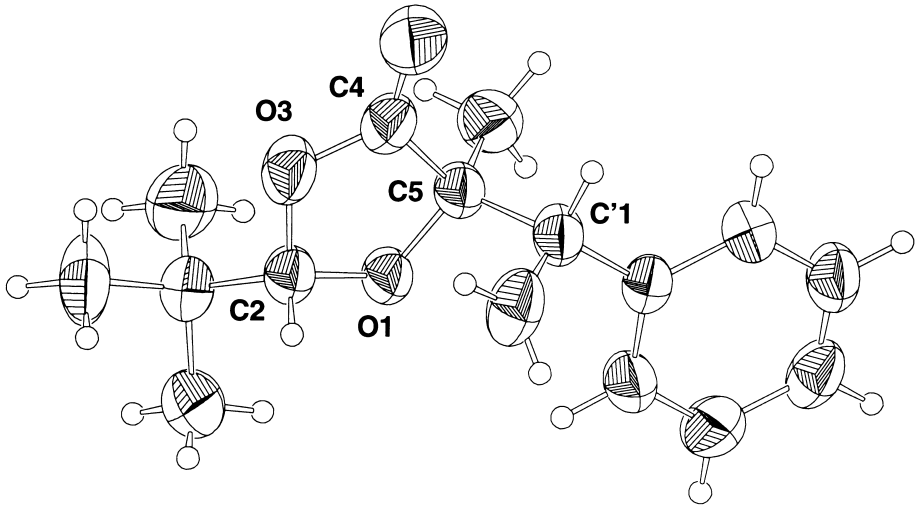
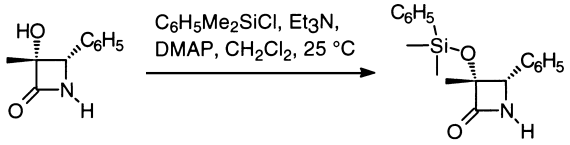



Figure 2. ORTEP of (1′*S*,2*S*,5*R*)-**6**




(*3R, 4S*)-**8** (*3R, 4S*)-**10**

Scheme 3. (3*R*,4*S*)-β-Lactam **10**

*2.1.2. Reaction with LDA*

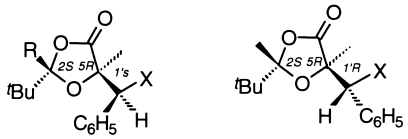
Next, we investigated the reaction of aldimine **2** with enolate **3a** using LDA as the base in the mixed solvent THF:HMPA=85:15. The addition reaction proved to be non-reproducible. In fact, variable mixtures of 3-hydroxy- and 3-trimethylsilyloxy-3-methyl-4-phenyl-β-lactams and imino-dioxolanones **4** and **5** were obtained in low yields with deleterious competing side reactions.[19]

*2.2. Reaction of enolate (2*S*)-**3b** and imine **2***

*2.2.1. Reaction with LHMDS*

Aldimine **2** was added at −90°C to the enolate of dioxolanone **1b** obtained with LHMDS in a THF:HMPA=85:15 mixed solvent. The reaction gave a mixture of imino-dioxolanones

(1′*S*,2*S*,5*R*)-**11**:(1′*R*,2*S*,5*R*)-**12**=2:1 (22%), a mixture of the corresponding amino-lactones (1′*S*,2*S*,5*R*)-**13**:(1′*R*,2*S*,5*R*)-**14**=9:1 (4%) (Fig. 3), a mixture of β-lactams (3*R*,4*S*)-**8**:(3*R*,4*R*)-**9**=4:1 (7%), and (3*R*,4*S*)-**15**:(3*R*,4*R*)-**16**=10:1 (44%) (Fig. 4).

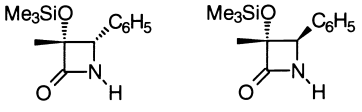



(*1'S,2S, 5R*)-**11** (*1'R,2S, 5R*)-**12**

(*1'S,2S, 5R*)-**13** (*1'R,2S, 5R*)-**14**

**11, 12**: X = N=CHC$_6$H$_5$;**13, 14**: X = NH$_2$

Figure 3. (2*S*,5*R*)-1′-Imino-dioxolanones **11**, **12** and (2*S*,5*R*)-1′-amino-dioxolanones **13**, **14**




(3*R, 4S*)-**15** (3*R, 4R*)-**16**

Figure 4. β-Lactams **15**, **16**

*2.2.2. Reaction with LDA*

Aldimine **2** was slowly added to the enolate **3b** obtained with LDA in the mixed solvent THF:HMPA=85:15 at −90°C. The reaction gave a mixture of the β-lactams (3*R*,4*S*)-**15**:*E*:(3*R*,4*R*)-**16**=6:1 (63%) and a 1:1 mixture of β-imino-lactones (1′*S*,2*S*,5*R*)-**11** and (1′*R*,2*S*,5*R*)-**12** (6%). Compound **15** was isolated by column chromatography ($SiO_2$, *n*-pentane:EtOAc, 8:2).[20] Alternatively, TBAF-induced O-desilylation of the crude reaction mixture, followed by chromatography, allowed the isolation of the β-lactams (3*R*,4*S*)-**8** (59%) and (3*R*,4*R*)-**9** (9%). It is worth noting that the reaction occurred with total enantiofacial selectivity. In fact, β-lactams (3*R*,4*S*)-**15** and (3*R*,4*R*)-**16** were obtained in 86% *ee* which is identical to the expected one on the basis of the *de* of the starting dioxolanone **1b**.

## 3. Conclusion

The above-described methodology appears to be a fairly direct approach to the synthesis of (3*R*,4*S*)-β-lactams **15** and **8** when they are synthesized from enolate **3b** using LDA as the base. In fact, **15** or **8** are obtained in good yields and with good *Z*:*E* diastereoselectivity (86:14). This is due to the greater stability of enolate **3b** compared to enolate **3a** in the presence of LDA. The methodology is quite useful to achieve complete (3*R*)-stereocontrol in the β-lactams since the single (1*S*,2*S*)-diastereomer of the starting reagents **1a** and **1b** can be easily obtained via recrystallization from pentane at −78°C[14b] and the addition reaction of the corresponding enolates **3a** and **3b** to imine **2** occurs from the face opposite to the *tert*-butyl substituent with full control of stereochemistry. The use of LHMDS as the base seems to inhibit the cyclization process, thus favoring the formation of the β-imino-dioxolanones with both enolates **3a** and **3b**. It is worth noting that β-imino-dioxolanones are in turn suitable intermediates for the synthesis of β-lactams via their facile hydrolysis to the corresponding amino-lactones followed by MeMgBr-induced cyclization.

## 4. Experimental

Solvents were dried according to published methods and distilled prior to use. All other reagents were commercially available compounds of highest purity. Melting points are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded on a 200 MHz VXR Varian spectrometer with $Me_4Si$ or $CHCl_3$ (in $CDCl_3$) as internal standards. Mass spectra were recorded on a Finnigan ion trap spectrometer with an ionization potential of 70 eV. Infrared spectra were recorded on a Nicolet 205-FT spectrometer. The dioxolanones were prepared according to the literature and were purified by distillation under vacuum. *N*-Trimethylsilylphenyl aldimine **2** was prepared according to literature procedures.[15] 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. Enantioselective analysis was performed on a Chiralcel OD column (Daicel 25×0.46 cm, I.D.). The mobile phase was *n*-hexane:2-propanol (97.5:2.5, v/v), at 1 mL/min, with UV and CD detection at 230 nm. CD spectra of (3*R*,4*S*)-β-lactams **8** and **15** (8 mM, solvent 2-propanol, 0.1 mm cell, room temperature) were obtained on a Jasco J 600 spectropolarimeter.

### *4.1. (1′*S,*2*S,*5*R*)- and (1′*R,*2*S,*5*R*)-2-(*tert-*Butyl)-5-(1′-benzylideneamino-1′-phenylmethyl)-5-methyl-1,3-dioxolan-4-ones [(1′*S,*2*S,*5*R*)-**4** and (1′*R,*2*S,*5*R*)-**5**]*

A THF solution (10 mL) of benzaldehyde (0.8 g, 7.83 mmol, 1 equiv.) was added to a THF solution (10 mL) of LHMDS (1.2 equiv.) at −10°C. Trimethylchlorosilane (7.80 mmol, 1.0 equiv.) was added after 20 min under stirring at 0°C. The resulting solution was cooled at −90°C and 3.8 mL of 1.0 M THF solution of LHMDS and 7.0 mL of HMPA were sequentially added. Finally, a THF solution (9.0 mL) of dioxolanone **1** (0.15 g, 3.16 mmol) was added over 4.0 h at −90°C via a syringe pump under stirring. The reaction mixture was treated with an aqueous solution of $NH_4Cl$. The organic layer was extracted two times with brine, dried over $Na_2SO_4$, and the solvent evaporated under reduced pressure. The (1′*S*,2*S*,5*R*):(1′*R*,2*S*,5*R*)=8.8:1 product distribution was calculated by $^1$H NMR analysis of the residue. Chromatography ($SiO_2$, EtOAc:*n*-hexane, 1:10) gave 0.45 g (1.28 mmol, 40.6%) of a mixture of (1′*S*,2*S*,5*R*)-**4** and (1′*R*,2*S*,5*R*)-**5**. IR ($CDCl_3$) cm$^{-1}$: 1780, 1643; MS, *m/z* 351 ($M^+$), 336, 307, 294, 238, 194. Anal. calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 75.05; H, 7.11; N, 4.06. (1′*S*,2*S*,5*R*)-**4**: $^1$H NMR ($CDCl_3$): δ 0.98 (s, 9H), 1.32 (s, 3H), 4.65 (s, 1H), 5.64 (s, 1H), 7.25–7.90 (m, 10H), 8.17 (s, 1H); $^{13}$C NMR ($CDCl_3$): δ 21.4, 23.4, 34.5, 79.2, 83.4, 110.5, 128.1, 128.3, 128.4, 128.6, 129.6, 131.1, 163.2, 175.7. (1′*R*,2*S*,5*R*)-**5**: $^1$H NMR ($CDCl_3$): δ 0.86 (s, 9H), 1.39 (s, 3H), 4.69 (s, 1H), 4.58 (s, 1H), 7.25–7.90 (m, 10H), 8.31 (s, 1H); $^{13}$C NMR ($CDCl_3$) relevant resonances at: δ 21.0, 23.3, 34.6, 80.2, 82.8, 109.5, 163.3, 174.1.

### *4.2. (1′*S,*2*S,*5*R*)- and (1′*R,*2*S,*5*R*)-2-(*tert-*Butyl)-5-(1′-amino-1′-phenylmethyl)-5-methyl-1,3-dioxolan-4-ones [(1′*S,*2*S,*5*R*)-**6** and (1′*R,*2*S,*5*R*)-**7**]*

An 8.8:1 mixture of (1′*S*,2*S*,5*R*)-**4** and (1′*R*,2*S*,5*R*)-**5** (0.60 g, 1.70 mmol) in 5.0 mL of acetone was treated at 20°C with 5.0 mL of a 1N aqueous solution of HCl under stirring for 6 h. The reaction mixture was diluted with 30 mL of acetone and the lactone amine chloridrate was filtered. The crude material was dissolved in 10 mL of an aqueous solution of 0.12 g of $K_2CO_3$ and stirred for 1 h. The aqueous solution was extracted with $CH_2Cl_2$. The organic layer was dried over $Na_2SO_4$, and the solvent evaporated under reduced pressure. Chromatography ($SiO_2$, *n*-pentane:EtOAc, 2:1) gave 0.264 g of (1′*S*,2*S*,5*R*)-**6** (37%) and 0.032 g of (1′*R*,2*S*,5*R*)-**7** (4%). (1′*S*,2*S*,5*R*)-**6**: mp 66–67°C; $^1$H NMR ($CDCl_3$): δ 0.95 (s, 9H), 1.23 (s, 3H), 1.70 (b, 2H), 4.07 (s, 1H), 5.30 (s, 1H), 7.30–7.40 (m, 5H); $^{13}$C NMR ($CDCl_3$): δ 22.2, 23.3, 34.8,

62.1, 83.6, 110.8, 127.8, 128.0, 128.5, 141.2, 176.0; IR ($CDCl_3$) $cm^{-1}$: 3500–3400, 1778; $[\alpha]_D^{25}$=+68.2 (c=1.37, $CDCl_3$); MS, *m/z* 263 ($M^+$), 219, 207, 106. Anal. calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.55; H, 8.11; N, 5.23. (1′*R*,2*S*,5*R*)-**7**: oil; $^1H$ NMR ($CDCl_3$): δ 0.86 (s, 9H), 1.49 (s, 3H), 2.0 (b, 2H), 4.20 (s, 1H), 4.64 (s, 1H), 7.30–7.40 (m, 5H); $^{13}C$ NMR ($CDCl_3$): δ 21.2, 23.2, 34.6, 60.3, 83.3, 109.6, 127.8, 128.1, 128.3, 140.1, 174.6; $[\alpha]_D^{25}$=+44.9 (c=1.60, $CDCl_3$).

### *4.3. Reaction of amino-dioxolanone (1′S,2S,5R)-**6** and MeMgBr*

MeMgBr (3.0 M in $Et_2O$, 0.6 mL, 1.8 mmol) was added to a solution of (1′*S*,2*S*,5*R*)-**6** (0.15 g, 0.57 mmol in 4 mL of $Et_2O$) at 0°C. The mixture was stirred at 25°C for 60 min. There was obtained 0.069 g (0.39 mmol, 68%) of (3*R*,4*S*)-**8**.

### *4.4. Reaction of enolate **3b** and aldimine **2***

A solution of 2.9 mmol of dioxolanone **2b** (*cis*:*trans*=93:7) in 6.0 mL of THF was added at −78°C to a solution of 4.35 mmol of LDA in 13.0 mL of THF. After 30 min the reaction mixture was cooled to −90°C and 5.0 mL of HMPA and 4.20 mmol of imine **2** were sequentially added over 60 min. The temperature was allowed to warm up to −60°C over a period of 2 h. The reaction was quenched at this temperature with a saturated aqueous solution of ammonium chloride and extracted twice with ethyl acetate. The organic layer was dried over $Na_2SO_4$, and the solvent evaporated under reduced pressure. A $^1H$ NMR spectrum of the crude reaction mixture revealed the presence of a mixture of (3*R*,4*S*)-**15**:*E*:(3*R*,4*R*)-**16**=6:1, and trace amounts of a 1:1 mixture of β-imino-lactones (1′*S*,2*S*,5*R*)-**11** and (1′*R*,2*S*,5*R*)-**12**. The TBAF-induced O-desilylation of the crude reaction mixture followed by chromatography allowed the isolation of the β-lactams (3*R*,4*S*)-**8** (59%) and (3*R*,4*R*)-**9** (9%).

### *4.5. (3R,4S)- and (3R,4R)-3-Hydroxy-3-methyl-4-phenyl-β-lactams [(3R,4S)-**8** and (3R,4R)-**9**]*

(3*R*,4*S*)-**8** from **1b**: mp 171–173°C; IR ($CDCl_3$) $cm^{-1}$: 3650, 3411, 1771; $^1H$ NMR ($CD_3COCD_3$): δ 1.58 (s), 2.75–2.85 (b, 1H), 4.61 (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; $[\alpha]_D^{25}$=+101 (c=0.5, $CD_3COCD_3$); MS, *m/z* 177 ($M^+$), 134, 106. Anal. calcd for $C_{10}H_{11}NO_2$: C, 67.75; H, 6.25; N, 7.90. Found: C, 67.84; H, 6.12; N, 7.83. (3*R*,4*R*)-**9** from **1b**: $^1H$ 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 19.0, 66.3, 88.0, 126.8, 128.3, 129.3, 139.2, 172.3.

### *4.6. (3R,4S)-3-Dimethylphenylsilyloxy-3-methyl-4-phenyl-β-lactam [(3R,4S)-**10**]*

A $CH_2Cl_2$ solution (5 mL) of a mixture of β-lactam (3*R*,4*S*)-**8** (0.05 g, 0.28 mmol), chlorodimethylphenylsilane (0.09 g, 0.53 mmol), triethylamine (0.08 g, 1.30 mmol) and 4-(dimethylamino)pyridine (0.005 g, 0.04 mmol) was reacted under stirring at 25°C for 5 h. The reaction mixture was treated with an aqueous solution of $NH_4Cl$. The organic layer was extracted two times with brine, dried over $Na_2SO_4$, and the solvent evaporated under reduced pressure. Chromatography ($SiO_2$, EtOAc:*n*-hexane, 1:10) gave 0.078 g (0.25 mmol, 91%) of (3*R*,4*S*)-**10**: oil; IR ($CDCl_3$) $cm^{-1}$: 1765; $^1H$ NMR ($CDCl_3$): δ 0.18 (s, 3H), 0.31 (s, 3H), 1.62 (s, 3H), 4.55 (s, 1H), 6.30 (bs, 1H), 7.20–7.40 (m, 10H); $^{13}C$ NMR ($CDCl_3$): δ −0.1, 0.2, 23.3, 40.9, 65.8, 87.5, 127.4, 127.5, 127.9, 128.2, 129.3, 133.2, 137.0, 138.3, 172.0; $[\alpha]_D^{25}$=+30 (c=0.5, $CDCl_3$); MS, *m/z* 311 ($M^+$), 268, 176. Anal. calcd for $C_{18}H_{21}NO_2Si$: C, 69.41; H, 6.80; N, 4.50. Found: C, 69.84; H, 6.72; N, 4.56. Lit.[11] (private communication): oil; IR (neat) $cm^{-1}$: 1763.5, 1235.7, 1120.5; $^1H$ NMR ($CDCl_3$): δ 0.16 (s, 3H), 0.30 (s, 3H), 1.62 (s, 3H), 4.54 (s, 1H), 6.58 (bs, 1H),

7.17–7.38 (m, 10H); $^{13}$C NMR ($CDCl_3$): δ −0.1, 0.2, 23.3, 40.9, 65.8, 87.5, 127.4, 127.5, 127.9, 128.2, 129.3, 133.2, 137.0, 138.3, 172.0; $[\alpha]_D^{20}$=+31.1 (c=0.74, $CHCl_3$).

### *4.7. (3*R*,4*S*)- and (3*R*,4*R*)-3-Trimethylsilyloxy-3-methyl-4-phenyl-β-lactams [(3*R*,4*S*)-**15** and (3*R*,4*R*)-**16**]*

(3*R*,4*S*)-**15** from **1b**: mp 86–88°C; IR ($CDCl_3$) cm$^{-1}$: 1764, 1236; $^1$H NMR ($CDCl_3$): δ −0.09 (s, 9H), 1.64 (s, 3H), 4.50 (s, 1H), 6.4–6.8 (b, 1H), 7.20–7.60 (m, 5H); $^{13}$C NMR ($CDCl_3$): δ 1.1, 23.3, 65.8, 87.3, 127.5, 127.8, 127.9, 137.1, 171.6; $[\alpha]_D^{25}$=48.0 (c=0.79, $CDCl_3$); MS, *m/z* 249 ($M^+$), 234, 206, 191, 73. Anal. calcd for $C_{13}H_{19}NO_2Si$: C, 62.71; H, 7.68; N, 5.62. Found: C, 62.84; H, 7.72; N, 5.53. (3*R*,4*R*)-**16**: $^1$H NMR ($CDCl_3$): δ 0.25 (s, 9H), 1.00 (s, 3H), 4.63 (s, 1H), 6.30–6.40 (b, 1H), 7.20–7.40 (m, 5H).

### *4.8. X-Ray crystallography*

Analyses were carried out on a single crystal of (1′*S*,2*S*,5*R*)-**6** obtained after slow evaporation of an ethyl acetate solution. Crystal data were collected at 293 K using an Enraf–Nonius CAD4 single crystal diffractometer with Mo-Kα radiation (λ=0.71073 Å). The structure was solved by direct methods using SHELXS. Refinements were carried out by full-matrix least squares of $F^2$ for all 2367 data using SHELXL-97. The refined Flack parameter did not allow the unambiguous experimental assignment of the absolute structure.

(1′*S*,2*S*,5*R*)-**6** ($C_{15}H_{21}NO_3$, *M*=263.33) monoclinic, space group $P2_1$, *a*=8.478(2) Å, *b*=6.3715(5) Å, *c*=14.363(4) Å, β=103.00(2)°, *V*=756.0(3) Å$^3$, *Z*=2, $D_c$=1.157 g/cm$^3$, μ(Mo-Kα)=0.080 mm$^{-1}$, final *R1*, *wR2* and *S* are 0.058, 0.148 and 1.02 for 177 parameters and 1418 unique observed reflections with $I>2\sigma(I)$. Tables of crystal data and structural refinement, final positional parameters, anisotropic thermal parameters, bond lengths and angles are available as supplementary material.

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