Pergamon

Tetrahedron 56 (2000) 5563–5570

TETRAHEDRON

On the Question of the Diastereoselective Alkylation of 4-Unsubstituted 3-Amino β-Lactams. A Concise Synthesis of α-Branched α-Amino β-Lactams and their Coupling with α-Amino Acid Esters

Claudio Palomo,[a,*] Jesus M. Aizpurua,[a] Regina Galarza,[a] Ana Benito,[a] Uttam K. Khamrai,[a] Unni Eikeseth[a] and Anthony Linden[b]

[a]*Departamento de Química Orgánica, Facultad de Química, Universidad del Pais Vasco, Apdo 1072, 20080 San Sebastián, Spain*
[b]*Organisch-chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland*

Received 27 September 1999; accepted 10 January 2000

Abstract—The reaction of [(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]acetic acid chloride with *N*-methylidene-bis-[(trimethylsilyl)methyl]amine and triethylamine in refluxing chloroform leads to a 4-unsubstituted β-lactam able to undergo highly asymmetric alkylations at the α-position of the β-lactam ring. The resulting adducts can be efficiently transformed into *N*-unsubstituted α-branched 3-amino β-lactams as the cyclisized forms of α-branched β-aminoalanines or transformed into their imide *N*-Boc derivatives, which are suitable substrates for non-proteinogenic peptide synthesis, by reaction with α-amino esters.

Introduction

The 4-unsubstituted azetidin-2-one ring is the key structural element of several β-lactam antibiotics.[1] Some of their well-known representatives (Fig. 1) are nocardicins **1**, monobactams **2**, and tabtoxin **3**.

Although there are a certain number of methods for the construction of the 4-unsubstituted β-lactam ring, i.e. the hydroxamate approach,[2] the ester enolate-imine condensation,[3] the ketene-imine cycloaddition[4] and the chromium carbene complex-imine reaction,[5] a general method for the synthesis of α-branched 3-amino 4-unsubstituted β-lactams is not available.[6] Owing to the presence of an α,α-disubstitution pattern, these compounds should be more resistant to both chemical and enzymatic hydrolysis than the parent monosubstituted β-lactams and, therefore, they should be suitable candidates for the study and design of new enzyme inhibitors.[7] The only work related to this idea has been reported by Georg and Schloss, who recently revealed that the racemic 3-amino β-lactam **4**, Fig. 2, is a time-independent inhibitor of α-chymotrypsin, carboxypeptidase Y, and cathepsin G.[8] More recently, we have reported the synthesis and conformational behaviour of the β-lactam peptide **5** which exhibits a type II β-turn motif both in the solid state and in solution ($CDCl_3$).[9]

Herein we report a concise general approach to this family of compounds which relies on our method for the synthesis of 3-amino β-lactams via the [2+2] cycloaddition reaction of aminoketene equivalents with *N*-[bis(trimethylsilyl)-methyl]imines.[10] In conjunction with this development, experimental evidence on the relative resistance of α-branched α-amino β-lactams towards ring opening by nitrogen nucleophiles is also documented.

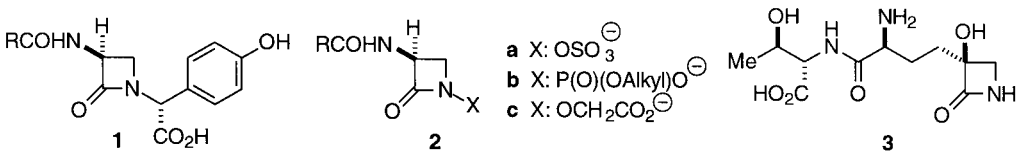


Figure 1. Structures of some representative 4-unsubstituted β-lactams.

Keywords: alkylation; β-lactams; α-amino acidesters.
* Corresponding author. E-mail: qoppanic@sc.ehu.es

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00406-3

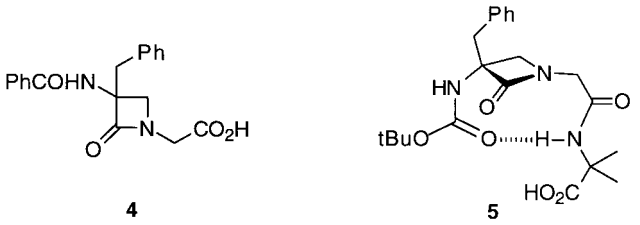
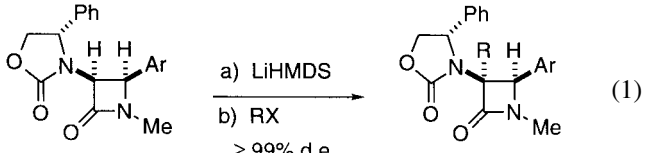
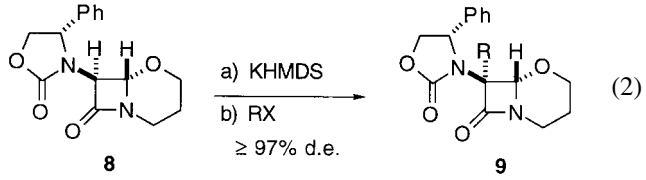


Figure 2. Some features of α-alkyl-α-amino-β-lactams. **4**: enzymatic inhibitor. **5** type-II β-turn nucleator.



(1)



(2)

Results and Discussion

The synthesis of α-branched 3-amino β-lactams is essentially a question of how an asymmetric alkylation at the α-position of a 3-amino 4-unsubstituted β-lactam could be performed efficiently. Literature precedents on the asymmetric alkylation of 3-amino β-lactams include only 4-substituted azetidinones and indicate that the stereochemical outcome of this reaction is governed by the relative orientation of the substituent at the C_4 position of the β-lactam ring.[11] For example, as shown in Eq. (1), alkylation of **6** takes place by the azetidinone face opposite to the Ar group, resulting in the formation of **7** as the sole reaction product.[12] However, it has also been found that the alkylation of **8** (Eq. (2)) proceeds by the same face as the C_4 substituent, leading to **9**.[13]

On the basis of these precedents, it was not possible to establish the stereodirecting effect exerted by the phenyloxalidinone moiety and, therefore, to predict whether the alkylation of a 4-unsubstituted β-lactam of type **10** (Fig. 3) would give **11** and/or **12**. Nonetheless, we anticipated that if the corresponding enolate of **10** could prevail in a W-like conformation, α-alkylated compound **12** should be obtained preferentially.

To test this hypothesis, we have developed the new chiral β-amino alaninate equivalent **16**. The preparation of **16** involved a completely stereoselective reaction of the imine **13**[14] with the Evans-Sjögren acid chloride **14**[15] and

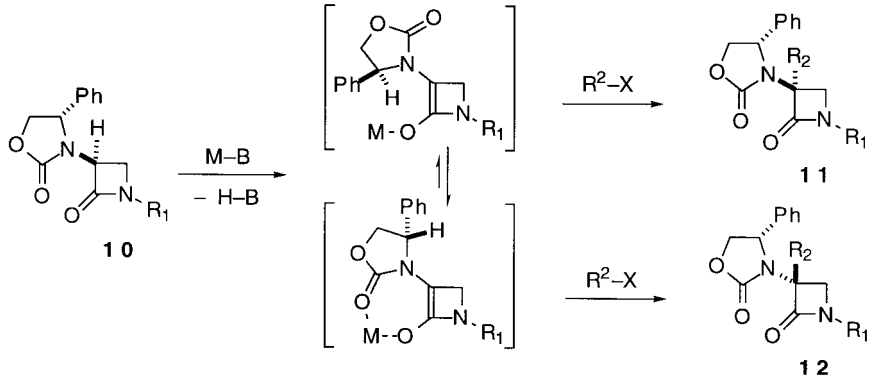
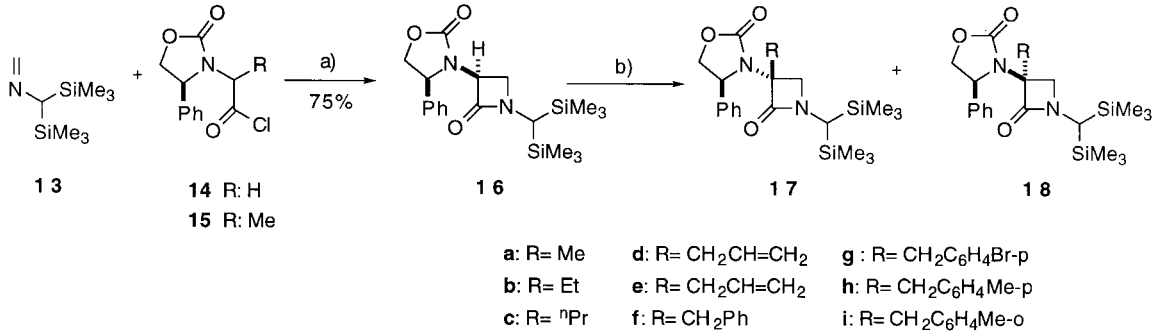


Figure 3. The alkylation of 4-unsubstituted 3-amido-β-lactams.

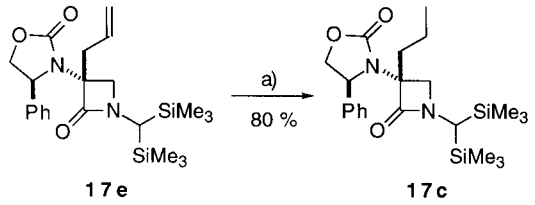


Scheme 1. (a) $CHCl_3$, NEt_3, 4 Å mol. sieves, reflux, 16 h, (b) LDA (1.5 equiv.), RX (5 equiv.), THF, −78°C→ rt, 16 h.

Table 1. Asymmetric alkylation of **16** (β-Lactam (1 mmol), THF (2 mL), LDA (1.5 equiv.), −78°C, 30 min; then R–X (3–5 equiv.), −78°C→rt, overnight)

Entry	R–X	**17/18**[a]	Yield of **17** (%)	Mp°C[b]	$[\alpha]_D^{25c}$
a	CH_3I	70/30	–[d]	Oil	–
b	CH_3CH_2I	71/29	41	95–96	−9.0
c	$CH_3CH_2CH_2Br$	80/20	40	Oil	+82.1
d	$(CH_3)_2CHCH_2Br$	91/9	62	99–100	−26.8
e	$CH_2{=}CHCH_2Br$	>98/2	70	111–112	−16.8
f	$C_6H_5CH_2Br$	>98/2	90	168–169	+21.5
g	*p*-$MeC_6H_4CH_2Br$	>98/2	75	143–145	+22.0
h	*o*-$MeC_6H_4CH_2Br$	>98/2	80	152–153	+32.1
I	*p*-$BrC_6H_4CH_2Br$	>98/2	75	157–158	+81.9

[a] Determined by integration of singlets between δ 2.75–2.45 ppm [*H*C(SiMe$_3$)$_2$].
[b] Crystallized from hexane.
[c] Measured in CH_2Cl_2 (c=1.0).
[d] Not isolated; the yield of the mixture **17/18** was 65%.



Scheme 2. (a) H_2 (1 atm.), Pd/C, EtOH, rt, 20 h.

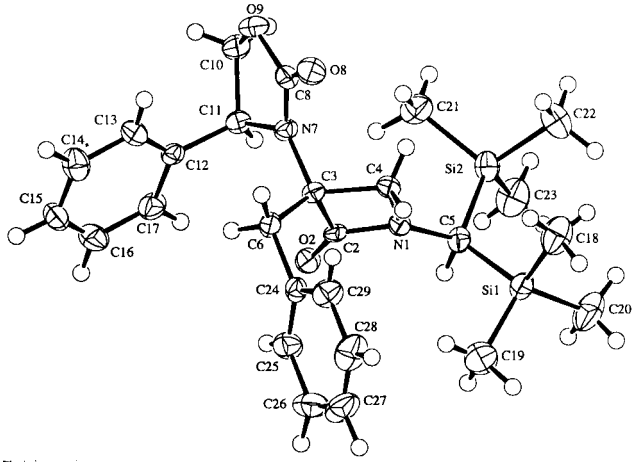


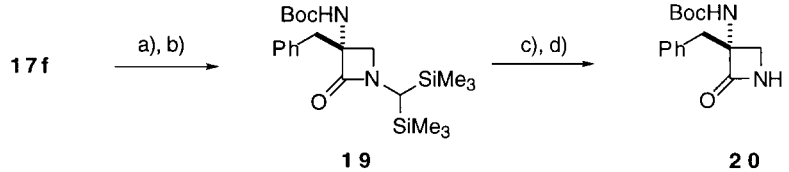
Figure 4. ORTEP plot of 3-benzyl-β-lactam **17f**.

triethylamine in refluxing chloroform for 16 h. Attempts to use formaldimine trimers derived from either benzylamine or trimethylsilylmethylamine instead of the imine **13** were unfruitful and did not yield the corresponding β-amino-alaninate equivalents. To the best of our knowledge, this is the first example of a monomeric formaldimine which can withstand high-temperature reaction conditions.[16]

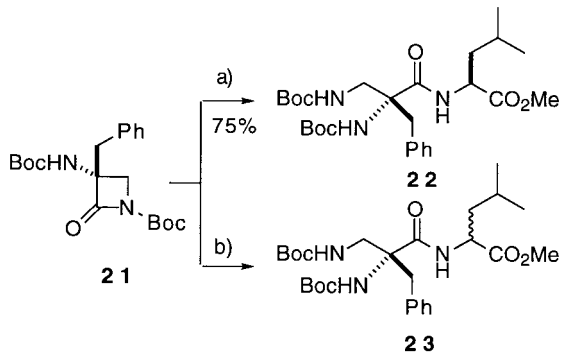
As Scheme 1 illustrates, the reaction of the lithium enolate of **16**, generated with LDA in THF as solvent, with a variety of alkylating agents gave the corresponding alkylated products **17/18** in good yields. Table 1 shows that the following two features are noteworthy. Firstly, the alkylation step can be performed by using both reactive and unreactive alkyl halides, although in the latter cases the yields are only moderate. Secondly, and most remarkable, the observed stereochemical outcome agrees with the proposed model, vide supra. As can be seen in Table 1, the ratio of isomers **17** and **18** seems to be dependent on the electrophile employed. Whereas alkyl halides usually gave mixtures of **17/18** in ratios ranging from 70:30 to 90:10, the use of allylic and benzylic halides led to the formation of the alkylated product **17** as virtually the sole diastereomer. Correlation of the stereochemical course of the reaction was primarily established by conversion of **17e** into **17c**, Scheme 2, and then by single-crystal X-ray crystallographic analyses of both **17b** and **17f** (Fig. 4).[17] The utility of this approach to α-branched 3-amino β-lactams can be further emphasized by the fact that the direct cycloaddition reaction of the imine **13** with the acid chloride **15**[18] and triethylamine in refluxing chloroform or benzene did not afford the corresponding cycloadducts **17a/18a**, therefore proving that this direct route seems to be impracticable.

Because *N*-unsubstituted β-lactams are of major interest, the cleavage of the *N*-bis(trimethylsilyl)methyl moiety was carried out using cerium(IV) ammonium nitrate (CAN).[19] For instance (Scheme 3), removal of the oxazolidinone moiety in **17f** and subsequent *N*-Boc protection of the resulting intermediate led to **19** in good yield over the two steps. Further exposure of **19** to CAN in acetonitrile-water for 45 min provided an *N*-formyl β-lactam in almost quantitative yield which was directly subjected to *N*-deformylation[20] to give the *N*-Boc β-lactam **20** in 56% overall yield from **17f**. Therefore, by this means, a variety of 3-amino 4-unsubstituted β-lactams with a quaternary stereogenic center at C_3 were obtained in a concise fashion and, most notably, from a single synthetic building block.

Besides their significance as building blocks of a new class of dipeptide mimics, vide supra, 3-amino β-lactams can also be viewed as the cyclisized forms of α,β-diamino acids.[21] Therefore, the next question we addressed was to establish whether these α-branched β-lactams might be coupled with α-amino acid esters thereby incorporating α-branched β-amino alanines as part of a peptide backbone.[22] With regard to this, we had previously observed that: a) the



Scheme 3. (a) Li (6 equiv.), NH_3(liq.), THF:*t*BuOH (10:1, v/v), −78°C, 5 min, then, NH_4Cl, (b) $(Boc)_2O$ (2 equiv.), CH_2Cl_2 rt, 16 h (c) $(NH_4)_2Ce(NO_3)_6$ (3 equiv.), MeCN–H_2O, 0°C, 45 min, (d) $NaHCO_3$, Na_2CO_3, Me_2CO, rt, 16 h.



Scheme 4. (a) (*S*)-$H_2NCH(^iPr)CO_2Me$ (1.2 equiv.), KCN (1.0 equiv.), rt, 19 h, (b) (±)-$H_2NCH(^iPr)CO_2Me$ (1.2 equiv.), DMF, KCN (1.0 equiv.), rt, 19 h.

presence of an electronwithdrawing substituent (Boc) at the β-lactam nitrogen atom was necessary to activate the nucleophilic ring opening with α-amino esters (neither **19** nor **20** were suitable substrates for such a reaction), and b) the ring opening of both 3-oxy and 3-amino-*N*-Boc-β-lactams was strongly influenced by the substitution pattern at C_4 position. Thus, while 3-oxy and 3-amino 4-monoalkylated *N*-Boc-β-lactams were efficiently coupled with α-amino acid esters in DMF without any additive or the need to use sodium azide as the promoter, the corresponding 4-dialkylated counterparts were unreactive under these conditions, and potassium cyanide was required to catalyze the coupling reaction.[23] Taking these observations into account, it was not surprising to observe that **21** (Scheme 4), prepared in 70% yield by treatment of **20** with $(Boc)_2O$ and a catalytic amount of *N*,*N*-dimethylaminopyridine in acetonitrile, upon treatment with (L)-LeuOMe either in the presence or the absence of sodium azide, was also resistant to β-lactam ring opening.

However, with the addition of potassium cyanide the coupling reaction gave the dipeptide **22** in 75% yield. On the other hand, the coupling reaction of **21** with racemic LeuOMe provided the diastereomeric mixture of dipeptides **23**. The HPLC chromatogram of the unpurified **22** was compared with that of the crude **23**, thus revealing that no epimerization at the α-center of the α-amino acid ester had occurred during the coupling reaction.

In summary, the synthesis of α-branched 3-amino 4-unsubstituted β-lactams can be performed efficiently via an asymmetric alkylation of a single 3-oxazolidinyl azetidin-2-one in which the configuration at the quaternary center is controlled by the absolute configuration of the oxazolidinone inducer. In addition, the resulting products could be incorporated directly into peptide fragments with the aid of potassium cyanide as promoter of the coupling.

Experimental

Melting points were determined with a capillary apparatus and are uncorrected. Proton nuclear magnetic resonance spectra (300 MHz) and ^{13}C spectra (75 MHz) were recorded at room temperature using $CDCl_3$ solutions, unless otherwise stated. All chemical shifts are reported as δ values (ppm) relative to residual $CDCl_3$ δ_H (7.26 ppm) and $CDCl_3$ δ_C (77.0 ppm) as internal standards, respectively. Mass spectra were obtained on a mass spectrometer (70 eV) using GC–MS coupling (column: fused silica gel, 15 m, 0.25 mm, 0.25 μm phase SPB-5). Optical rotations were measured at 25±0.2°C in methylene chloride unless otherwise stated. HPLC analyses were performed on a preparative column (25 cm, 3.0 cm 7 μm phase Lichrosorb-Si60) with flow rates of 10 mL/min and using a UV detector (254 nm). Flash chromatography was executed with Merck Kiesegel 60 (230–400 mesh) using mixtures of ethyl acetate and hexane as eluants. Acetonitrile and hexane were dried and purified by distillation. Tetrahydrofuran was distilled over sodium and benzophenone (indicator) and diisopropylamine was distilled over KOH pellets prior to use. Methylene chloride and chloroform were shaken with concentrated sulfuric acid, dried over potassium carbonate and distilled. Commercially available compounds were used without further purification, but allyl iodide and benzyl bromides were distilled just before using. (3*S*)-1-bis(trimethylsilyl)methyl-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one **16** was prepared according to literature procedure.[10b]

General procedure for the alkylation of β-lactam 16

LDA was formed by slow addition of 1.4 M *n*-butyllithium (3.12 mL, 6 mmol) to a cooled (−78°C) solution of diisopropylamine (0.84 mL, 6 mmol) in THF (10 mL) under a nitrogen atmosphere and stirring at the same temperature for 30 min. A solution of the β-lactam **16** (1.56 g, 4 mmol) in THF (8 mL) was added dropwise and the mixture was stirred for 1 h at −78°C. Finally, the corresponding alkyl halide (20 mmol, freshly distilled) was added dropwise and the dry-ice/acetone bath was allowed to reach room temperature overnight. Taking up over methylene chloride (30 mL), washing with sat. NH_4Cl (15 mL) and water (15 mL), drying ($MgSO_4$) and evaporation afforded the crude 3-alkyl β-lactam, which was purified by flash chromatography (silica gel, eluant: hexane/EtOAc 15/1).

(3*R*) and (3*S*)-1-[Bis(trimethylsilyl)methyl]-3-methyl-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azeti din-2-ones (17a) and (18a). The general procedure was followed, using methyl iodide (1.36 mL, 20 mmol) as the alkyl halide, to give a 70/30 mixture of (**17a**) and (**18a**) that could not be separated by column chromatography. Yield 65%. Preparative HPLC allowed the separation of an analytical sample of (17a): IR (KBr) ν 1740 cm^{-1} (C=O), 842 (C–Si). MS (*m/z*, rel. int.) 68(40), 73(55), 104(38), 118(100), 138(13), 202(26), 203(40), 276(14), 389 (M^+-15). ^1H NMR ($CDCl_3$, δ ppm) 7.47–7.33 (m, 5H); 5.01–4.98 (m, 3H, *J*=2.2 Hz, *J*=8.7 Hz); 4.62 (t, 1H, *J*=8.7 Hz); 4.30 (dd, 1H, *J*=2.2 Hz, *J*=8.7 Hz); 3.73 (d, 1H, *J*=6.1 Hz); 3.27 (d, 1H, *J*=6.6 Hz); 2.73 (s, 1H); 1.18 (s, 3H); 0.15 (s, 9H); 0.12 (s, 9H). ^{13}C NMR ($CDCl_3$, δ ppm) 165.8, 158.0, 140.2, 129.0, 128.8, 127.0, 71.0, 66.9, 59.6, 57.1, 36.7, 19.2, −0.3.

(3*R*)-1-[Bis(trimethylsilyl)methyl]-3-ethyl-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (17b). The general procedure was followed using ethyl iodide (1.60 mL, 20 mmol) as the alkyl halide. Yield 41%. Mp: 95–96°C (hexane). $[\alpha]_D^{25}=-9.0$ (*c*=1.0, CH_2Cl_2). IR (KBr) ν

1740 cm^{-1} (C═O), 843 (C–Si). MS (*m/z*, rel. int.) 55(19), 73(75), 82(20), 91(9), 104(100), 217(11). ^1H NMR ($CDCl_3$, δ ppm) 7.50–7.34 (m, 5H); 5.07 (dd, 1H, *J*=2.0 Hz, *J*=8.2 Hz); 4.60 (t, 1H, *J*=8.4 Hz); 4.34 (dd, 1H, *J*=2.0 Hz, *J*=8.6 Hz); 3.66 (d, 1H, *J*=6.6 Hz); 3.46 (d, 1H, *J*=6.6 Hz); 2.74 (s, 1H); 1.60–1.49 (m, 1H); 1.27–1.12 (m, 1H); 0.78 (t, 3H, *J*=7.3 Hz); 0.15 (s, 9H); 0.13 (s, 9H). ^{13}C NMR ($CDCl_3$, δ ppm) 165.0, 156.8, 140.4, 128.8, 128.7, 127.2, 72.0, 71.1, 59.5, 58.1, 37.0, 25.2, 8.8, −0.3, −0.4. Anal. calcd for $C_{21}H_{35}N_2O_3Si_2$ (419.56): C, 60.11; H, 8.42; N, 6.67. Found: C, 60.32; H, 8.50; N, 6.51.

(3*R*)-1-[Bis(trimethylsilyl)methyl]-3-(3-methylpropyl)-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (17d). The general procedure was followed using isobutyl bromide (2.17 mL, 20 mmol) as the alkyl halide. Yield 62%. Mp: 99–100°C (hexane). $[\alpha]_D^{25}$=−26.8 (*c*=0.59, CH_2Cl_2). IR (KBr) ν 1738 cm^{-1} (C═O), 848 (C–Si). MS (*m/z*, rel. int.) 68(96), 73(100), 104(99), 118(39), 204(98), 205(41), 246(37). ^1H NMR ($CDCl_3$, δ ppm) 7.47–7.33 (m, 5H); 5.19 (dd, 1H, *J*=2.3 Hz, *J*=8.4 Hz); 4.61 (t, 1H, *J*=8.6 Hz); 4.41 (dd, 1H, *J*=2.3 Hz, *J*=8.4 Hz); 3.89 (d, 1H, *J*=6.8 Hz); 3.50 (d, 1H, *J*=6.8 Hz); 2.70 (s, 1H); 1.63–1.30 (m, 3H); 0.89 (d, 3H, *J*=6.3 Hz); 0.49 (d, 3H, *J*=6.3 Hz); 0.15 (s, 9H); 0.12 (s, 9H). ^{13}C NMR ($CDCl_3$, δ ppm) 165.9, 140.4, 128.8, 127.7, 71.0, 70.7, 59.5, 54.5, 41.9, 37.0, 24.1, 22.9, −0.2, −0.3. Anal. calcd for $C_{23}H_{38}N_2O_3Si_2$(446.74): C, 61.84; H, 8.57; N, 6.27. Found: C, 61.51; H, 8.25; N, 6.40.

(3*R*)-3-Allyl-1-[bis(trimethylsilyl)methyl]-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (17e). The general procedure was followed using allyl bromide (1.73 mL, 20 mmol) as the alkyl halide. Yield 70%. Mp: 111–112°C (hexane). $[\alpha]_D^{25}$=−16.8 (*c*=1.0, CH_2Cl_2). IR (KBr) ν 1753, 1734 cm^{-1} (C═O), 842 (C–Si). MS (*m/z*, rel. int.) 73(75), 92(29), 144(86), 170(67), 184(61), 193(35), 229(100), 302(48), 416(60), 429(16). ^1H NMR ($CDCl_3$, δ ppm) 7.53–7.26 (m, 5H); 5.65–5.49 (m, 1H); 5.10–4.98 (m, 3H); 4.59 (t, 1H, *J*=8.6 Hz); 4.35 (dd, 1H, *J*=2.0 Hz, *J*=8.6 Hz); 3.59 (d, 1H, *J*=6.4 Hz); 3.49 (d, 1H, *J*=6.5 Hz); 2.70 (s, 1H); 2.31 (dd, 1H, *J*=8.5 Hz, *J*=14.2 Hz); 1.83 (dd, 1H, *J*=6.1 Hz, *J*=14.1 Hz); 0.13 (s, 9H); 0.11 (s, 9H). ^{13}C NMR ($CDCl_3$, δ ppm) 164.4, 156.7, 140.1, 131.7, 129.0, 127.4, 119.9, 71.2, 70.3, 59.6, 52.9, 37.1, 36.4, −0.2, −0.3. Anal. calcd for $C_{22}H_{34}N_2O_3Si_2$ (430.56): C, 61.37; H, 7.97; N, 6.50. Found: C, 61.55; H, 8.15; N, 6.23.

(3*R*)-3-Benzyl-1-bis(trimethylsilyl)methyl-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (17f). The general procedure was followed using benzyl bromide (2.38 mL, 20 mmol) as the alkyl halide. Yield 90%. Mp: 168–169°C (hexane). $[\alpha]_D^{25}$=+21.5 (*c*=1.0, CH_2Cl_2). IR (KBr) ν 1737, 1730 cm^{-1} (C═O), 846 (C–Si). MS (*m/z*, rel. int.) 73(15), 93(11), 104(16), 144(22), 221(19), 235(24), 280(100), 466(15), 481(1.2). ^1H NMR ($CDCl_3$, δ ppm) 7.70–7.17 (m, 10H); 5.18 (dd, 1H, *J*=8.1 Hz, *J*=1.8 Hz); 4.64 (t, 1H, *J*=8.5 Hz); 4.43 (dd, 1H, *J*=8.7 Hz, *J*=1.9 Hz); 3.52 (d, 1H, *J*=6.6 Hz); 3.44 (d, 1H, *J*=6.4 Hz); 2.85 (d, 1H, *J*=13.7 Hz); 2.52 (s, 1H); 2.24 (d, 1H, *J*=13.7 Hz); 0.00 (s, 9H); −0.12 (s, 9H). ^{13}C NMR ($CDCl_3$, δ ppm) 164.0, 156.7, 140.1, 134.8, 130.5, 134.8, 130.5, 129.0, 128.5, 127.7, 126.9, 72.0, 71.1, 59.7, 52.1, 37.4, 37.2, −0.6. Anal. calcd for $C_{26}H_{36}N_2O_3Si_2$ (480.62): C, 64.97; H, 7.56; N, 5.83. Found: C, 64.89; H, 7.60; N, 5.92.

(3*R*)-1-[Bis(trimethylsilyl)methyl]-3-[(4-methylphenyl)-methyl]-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl] azetidin-2-one (17g). The general procedure was followed using *p*-methylbenzyl bromide (3.70 g, 20 mmol) as the alkyl halide. Yield 75%. Mp: 143–145°C (hexane). $[\alpha]_D^{25}$=+22.0 (*c*=1.0, CH_2Cl_2). IR (KBr) ν 1731 cm^{-1} (C═O), 840 (C–Si). MS (*m/z*, rel. int.) 73(100), 91(14), 104(32), 105(21), 131(17), 158(12), 293(53), 294(11). ^1H NMR ($CDCl_3$, δ ppm) 7.63–7.59 (m, 2H); 7.42–6.90 (m, 7H); 5.13 (dd, 1H, *J*=1.1 Hz, *J*=6.5 Hz); 4.60 (t, 1H, *J*=8.5 Hz); 4.42 (dd, 1H, *J*=1.7 Hz, *J*=8.6 Hz); 3.46 (d, 1H, *J*=6.5 Hz); 3.40 (d, 1H, *J*=6.4 Hz); 2.77 (d, 1H, *J*=13.5 Hz); 2.48 (s, 1H); 2.21 (s, 3H); 2.16 (d, 1H, *J*=13.9 Hz); −0.03 (s, 9H); −0.20 (s, 9H). ^{13}C NMR ($CDCl_3$, δ ppm) 164.1, 156.7, 140.1, 136.5, 131.6, 130.4, 129.2, 129.0, 127.7, 72.0, 71.2, 59.8, 52.1, 37.3, 36.8, 20.8, −0.6, −0.8. Anal. calcd for $C_{27}H_{38}N_2O_3Si_2$(494.92): C, 65.52; H, 7.75; N, 5.66. Found: C, 65.01; H, 7.94; N, 5.83.

(3*R*)-1-[Bis(trimethylsilyl)methyl]-3-[(2-methylphenyl)-methyl]-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (17h). The general procedure was followed using *o*-methylbenzyl bromide (3.70 g, 20 mmol) as the alkyl halide. Yield 80%. Mp: 152–153°C (hexane). $[\alpha]_D^{25}$=+32.1 (*c*=1.0, CH_2Cl_2). IR (KBr) ν 1728 cm^{-1} (C═O), 840 (C–Si). MS (*m/z*, rel. int.) 73(100), 91(13), 103(15), 104(25), 130(82), 158(7), 293(34), 294(8). ^1H NMR ($CDCl_3$, δ ppm) 7.66–7.62 (m, 3H); 7.41–7.35 (m, 2H); 7.05–7.00 (m, 2H); 5.15 (dd, 1H, *J*=1.5 Hz, *J*=8.1 Hz); 4.64 (t, 1H, *J*=8.3 Hz); 4.45 (dd, 1H, *J*=1.5 Hz, *J*=8.8 Hz); 3.48 (d, 1H, *J*=6.6 Hz); 3.34 (d, 1H, *J*=6.6 Hz); 2.88(d,1H, *J*=14.1 Hz); 2.51 (s, 1H); 2.20 (d, 1H, *J*=13.4 Hz); 2.18 (s, 3H); −0.02 (s, 9H); −0.19 (s, 9H). ^{13}C NMR ($CDCl_3$, δ ppm) 164.2, 156.8, 140.3, 137.5, 133.4, 131.4, 130.5, 129.0, 127.8, 127.2, 126.1, 71.9, 71.2, 59.9, 52.2, 37.5, 34.3, 19.5, −0.6, −0.7. Anal. calcd for $C_{27}H_{38}N_2O_3Si_2$ (494.92): C, 65.52; H, 7.75; N, 5.66. Found: C, 65.05; H, 7.94; N, 5.80.

(3*R*)-1-[Bis(trimethylsilyl)methyl]-3-[(4-bromophenyl)-methyl]-3-[(4*S*)-2-oxo-4-phenyloxazolidin-3-yl]azetidin-2-one (17i). The general procedure was followed using *p*-methylbenzyl bromide (5.00 g, 20 mmol) as the alkyl halide. Yield 75%. Mp: 157–158°C (hexane). $[\alpha]_D^{25}$=+18.9 (*c*=1.0, CH_2Cl_2). IR (KBr) ν 1733 cm^{-1} (C═O), 841 (C–Si). MS (*m/z*, rel. int.) 73(100), 91(7), 103(14), 104(26), 116(15), 357(18), 359(18). ^1H NMR ($CDCl_3$, δ ppm) 7.65–7.28 (m, 5H); 6.93 (d, 2H, *J*=8.3 Hz); 5.14 (dd, 1H, *J*=1.7 Hz, *J*=8.2 Hz); 4.63 (t, 1H, *J*=8.2 Hz); 4.46 (dd, 1H, *J*=1.4 Hz, *J*=8.8 Hz); 3.50 (d, 1H, *J*=6.7 Hz); 3.37 (d, 1H, *J*=6.6 Hz); 2.80 (d, 1H, *J*=13.5 Hz); 2.49 (s, 1H); 2.32 (d, 1H, *J*=13.5 Hz); 0.00 (s, 9H); −0.16 (s, 9H). ^{13}C NMR ($CDCl_3$, δ ppm) 164.2, 156.7, 140.0, 133.8, 132.3, 131.7, 129.1, 127.7, 121.2, 71.7, 59.8, 52.3, 37.6, 36.7, −0.7, −0.6. Anal. calcd for $C_{26}H_{35}N_2O_3Si_2Br$ (559.61): C, 55.80; H, 6.32; N, 5.00. Found: C, 56.01; H, 6.25; N, 5.12.

Hydrogenation reaction of 17e: synthesis of (3*R*)-1-bis(trimethylsilyl)methyl-3-[(4*S*)-2-oxo-4-phenyloxa-

zolidin-3-yl]-3-propylazetidin-2-one (17c). A suspension of β-lactam **17e** (0.86 g, 2 mmol) and Pd (10%)/C (0.086 g) in anhydrous methanol (8 mL) was saturated with hydrogen (1 atm.) at room temperature for 20 h. Then, the solution was filtered over celite, the solvents were evaporated and the resulting crude was purified by preparative HPLC (eluant: hexane/EtOAc, 1/8). Yield 48%. Colorless oil. $[\alpha]_D^{25}=+82.1$ (c=0.61, CH_2Cl_2). IR (KBr) ν 1739 cm^{-1} (C=O), 844 (C–Si). MS (*m/z*, rel. int.) 74(39), 105(41), 119(48), 170(11), 203(100), 231(32), 418 (M^+-15). ^1H NMR ($CDCl_3$, δ ppm) 7.55–7.30 (m, 5H); 5.10 (dd, 1H, J=2.1 Hz, J=8.3 Hz); 4.61 (t, 1H, J=8.4 Hz); 4.37 (dd, 1H, J=2.2 Hz, J=8.6 Hz); 3.27 (d, 1H, J=6.6 Hz); 3.43 (d, 1H, J=6.6 Hz); 2.73 (s, 1H); 1.41–0.84 (m, 4H); 0.63 (t, 3H, J=6.7 Hz); 0.13 (s, 9H); 0.01 (s, 9H). ^{13}C NMR ($CDCl_3$, δ ppm) 165.3, 156.9, 140.3, 128.9, 128.8, 127.3, 71.0, 59.5, 53.7, 36.9, 34.8, 17.6, 13.8, −0.3, −0.4.

(3*R*)-3-Benzyl-1-bis(trimethylsilyl)methyl-3-(*tert*-butoxycarbonylamino)azetidin-2-one (19). Compound **17f** (0.53 g, 1.1 mmol) was submitted to deprotection of the oxazolidinone moiety[15] to yield (3*R*)-3-amino-3-benzyl-1-bis(trimethylsilyl)methylazetidin-2-one (0.33 g, 98%, 1 mmol). This compound was dissolved in anhydrous CH_2Cl_2 (5 mL), $(Boc)_2O$ (0.44 g, 2 mmol) was added and the mixture was stirred at room temperature for 20 h. Then, the mixture was washed successively with $NaHSO_3$ (20%) (3 mL) and $NaHCO_3$ (sat. sol. 3 mL) and the resulting organic layer was dried over $MgSO_4$. The solvents were evaporated and the resulting crude was purified by column chromatography (eluant: hexane/EtOAc 8/1). An analytical sample was obtained by preparative HPLC (eluant: hexane/EtOAc 6/1, r.t.=9.12 min). Oil. Yield 74%. $[\alpha]_D^{25}=-13.1$ (c=1.0, CH_2Cl_2). IR (KBr) ν 3298, 2949 cm^{-1} (NH),1730, 1699 cm^{-1} (C=O), 842 (C–Si). MS (*m/z*, rel. int.) 73(20), 92(27), 134(14), 177(100), 207(21), 233(18), 282(210, 346(150), 364 (M^+-56,21) ^1H NMR ($CDCl_3$, δ ppm) 7.28–7.22 (m, 5H); 5.21 (s, 1H); 3.54 (d, 1H, J=5.7 Hz); 3.40 (d, 1H, J=5.7 Hz); 3.20 (s, 2H); 2.60 (s, 1H); 1.42 (s, 9H); 0.04 (s, 9H); −0.09 (s, 9H). ^{13}C NMR ($CDCl_3$, δ ppm) 166.7, 154.8, 135.5, 130.3, 128.4, 126.8, 79.9, 68.0, 54.0, 38.8, 37.0, 28.2, −0.4, −0.5.

(3*R*)-3-Benzyl-3-(*tert*-butoxycarbonylamino)azetidin-2-one (20). A solution of cerium(IV) ammonium nitrate (CAN, 1.64 g, 3 mmol) in H_2O (2.5 mL) was added dropwise to a stirred solution of the 1-bis(trimethylsilyl)methyl-β-lactam **22** (0.42 g, 1 mmol) in CH_3CN (6 mL) cooled at 0°C. The mixture was stirred for 45 min at the same temperature, poured into EtOAc (10 mL) and washed successively with water (10 mL) and $NaHCO_3$ (sat. sol. 10 mL). The resulting organic phase was dried over $MgSO_4$, the solvents were evaporated and the resulting crude was purified by column chromatography (eluant hexane/EtOAc 4/1) to afford the intermediate *N*-formyl derivative (yield: 80%). This compound was disolved in acetone (6.0 mL) containing $NaHCO_3$ (sat. soln. 3.32 mL) and Na_2CO_3 (0.056 g, 0.2 mmol) and the mixture was stirred for 24 h. at room temperature. On completion, the mixture was filtered through a pad of silica gel which was additionally washed with EtOAc (15 mL). The organic solution was dried over $MgSO_4$ and evaporated to afford a crude which was purified by column chromatography (eluant: EtOAc). Yield: 70%. Mp: 108–110. $[\alpha]_D^{25}=+30.7$ (c=1.0, CH_2Cl_2). IR (KBr) ν 3273, 2961 cm^{-1} (NH), 1759, 1701 cm^{-1} (CO). MS (*m/z*, rel. int.) 57(9), 91(24), 92(29), 116(10), 133(12), 177 (M^+-Boc), 233(4), 265(1). ^1H NMR ($DMSO_{d6}$, 90°C, δ ppm) 7.43 (s, 1H); 7.29 (s, 5H); 6.61 (s, 1H); 3.38 (d, 1H, J=5.3 Hz); 3.12 (d, 1H, J=5.3 Hz); 3.06 (s, 2H); 1.41 (s, 9H). ^{13}C NMR ($CDCl_3$, δ ppm) 169.6, 154.3, 134.7, 130.0, 128.6, 127.2, 80.4, 69.2, 47.7, 39.5, 28.2. Anal. calcd for $C_{15}H_{20}N_2O_3$ (276.35): C, 65.19; H, 7.13; N, 10.13. Found: C, 65.13; H,7.44; N, 9.80.

(3*R*)-3-Benzyl-1-*tert*-butoxycarbonyl-3-(*tert*-butoxycarbonylamino)azetidin-2-one (21). $(Boc)_2O$ (0.26 g, 1.2 mmol) and DMAP (0.012 g, 0.1 mmol) were added to a solution of the NH-β-lactam **20** (0.28 g, 1 mmol) in anhydrous acetonitrile (5 mL) and the mixture was stirred for 20 h at room temperature. The reaction mixture was poured into CH_2Cl_2 (10 mL) and washed successively with $NaHSO_3$ (20% soln. 8 mL) and $NaHCO_3$ (sat. soln. 8 mL). The resulting organic layer was dried over $MgSO_4$, the solvents were evaporated and the resulting crude was purified by column chromatography (eluant: hexane/EtOAc 5/1). Yield: 70%. Mp: 170–172°C (hexane/EtOAc). $[\alpha]_D^{25}=+25.8$ (c=1.0, CH_2Cl_2). IR (KBr) ν 3334, 2965 cm^{-1} (NH), 1800, 1715, 1699 cm^{-1} (C=O). MS (*m/z*, rel. int.) 57(17), 91(29), 92(34), 116(14), 133(15), 177(100), 219(11), 247(7), 352(7), 254(6). ^1H NMR ($DMSO_{d6}$, 90°C, δ ppm) 7.28 (s, 8H); 6.99 (s, 5H); 3.68 (d, 1H, J=6.6 Hz); 3.48 (d, 1H, J=6.6 Hz); 3.09 (s, 2H); 1.41 (s, 9H); 1.36 (s, 9H). ^{13}C NMR ($CDCl_3$, δ ppm) 166.3, 153.9, 148.1, 133.8, 129.8, 128.9, 127.7, 83.3, 66.7, 50.3, 39.6, 28.1, 28.0. Anal. calcd for $C_{20}H_{28}N_2O_3$ (376.48): C, 63.80; H, 7.51; N, 7.44. Found: C, 63.91; H, 7.59; N, 7.47.

(2*R*)-2-Benzyl-2,3-di-*tert*-butoxycarbonylamino-*N*-[L-Val-(OMe)]-propanamide (22). KCN (0.065 g, 1 mmol) and (*S*)-valine methyl ester (0.17 g, 1.2 mmol) were added to a solution of **21** (1 mmol, 0.38 g) in DMF (3 mL). The mixture was stirred at room temperature for 19 h and the solution was poured into Et_2O (10 mL). Successive washing with NaCl (sat. soln. 2×15 mL), 0.1 M HCl (8 mL) and $NaHCO_3$ (sat. soln. 8 mL), drying ($MgSO_4$) of the organic phase and solvent evaporation resulted in a crude product which was purified by crystallization. Mp: 102–104°C (hexane). Yield 75%. $[\alpha]_D^{25}=-16.5$ (c=0.17, CH_2Cl_2). IR (KBr) ν 3290, 2945 cm^{-1} (NH), 1710, 1658 cm^{-1} (CO). ^1H NMR (CD_3OD, 50°C, δ ppm) 7.27–7.18 (m, 5H); 4.50 (t, 1H, J=7.0 Hz); 3.74 (s, 3H); 3.49 (d, 1H, J=11.5 Hz); 3.44 (d, 1H, J=10.1 Hz); 3.42 (d, 1H, J=11.4 Hz); 3.15 (d, 1H, J=11.4 Hz); 1.80–1.62 (m, 3H); 1.48 (s, 9H); 1.42 (s, 9H); 0.93 (d, 6H, J=6.0 Hz). ^{13}C NMR (CD_3OD, δ ppm) 175.0, 174.5, 158.4, 156.3, 137.4, 131.9, 129.1, 127.8, 80.7, 64.3, 52.9, 52.5, 46.3, 41.0, 37.3, 28.7, 28.6, 25.6, 23.4, 21.7. Anal. calcd for $C_{27}H_{43}N_3O_7$(521.70): C, 62.15; H, 8.32; N, 8.05. Found: C, 62.23; H, 8.30; N, 7.97.

Acknowledgements

Financial support of this work by the Comisión Interministerial de Ciencia y Tecnología (Project: SAF 98-0159-CO2-01) and a grant from Gobierno Vasco to A. B. are gratefully acknowledged.

References

1. For some reviews on β-lactam antibiotics, see: (a) Dürkheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180. (b) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vols. 1–3. (c) Southgate, R.; Branch, C.; Coulton, S.; Hunt, E. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Lukacs, G., Ed.; Springer: Berlin, 1993; Vol. 2, p 621. (d) Southgate, R. *Contemp. Org. Synth.* **1994**, *1*, 417.

2. For reviews, see: (a) Hanessian, S.; Sahoo, S. P.; Couture, C.; Wyss, H. *Bull. Soc. Chim. Belg.* **1984**, *93*, 571. (b) Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49.

3. (a) Overman, L. E.; Osawa, T. *J. Am. Chem. Soc.* **1985**, *107*, 1698. For reviews on the ester enolate–imine approach, see: (b) Hart, D. J.; Ha, D. C. *Chem. Rev.* **1989**, *89*, 1447. (c) Georg, G. I. In *Studies in Natural Product Chemistry*; Rahman, A.-ur, Ed.; Elsevier: Amsterdam, 1989; Vol. 4, p 431.

4. (a) Curran, W. V.; Sassiver, M. L.; Ross, A. S.; Fields, T. L.; Boothe, J. H. *J. Antibiot.* **1982**, *35*, 329. (b) Kamiya, T.; Hashimoto, M.; Nakaguchi, O.; Oku, T. *Tetrahedron* **1979**, *35*, 323. (c) Nakaguchi, O.; Oku, T. Takeno, H.; Hashimoto, M. Kamiya, T. *Chem. Pharm. Bull.* **1987**, *35*, 3985. (d) Arrieta, A.; Lecea, B.; Cossio, F. P.; Palomo, C. *J. Org. Chem.* **1988**, *53*, 3784. For recent reviews on ketene–imine cycloadditions, see: (e) Ghosez, L.; Marchand-Brynaert, S. In *Comprehensive Organic Synthesis*; Trost, B., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 85. (f) Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I, Ed.; VCH: New York, 1993, p 295. (g) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223.

5. (a) Hegedus, L. S.; D'Andrea, S. *J. Org. Chem.* **1988**, *53*, 3133. (b) Narukawa, Y.; Juneau, K. N.; Snustad, D.; Miller, D. B.; Hegedus, L. S. *J. Org. Chem.* **1992**, *57*, 5453. (c) Alcaide, B.; Casarrubios, L.; Dominguez, G.; Sierra, M. A. *J. Org. Chem.* **1994**, *59*, 7934. For leading references on chromium carbene complex photochemistry, see: (d) Hegedus, L. S. *Acc. Chem. Res.* **1995**, *28*, 299. For the application of organometallic reagents in β-lactam synthesis, see: (e) Barret, A. G. M.; Sturgess, M. A. *Tetrahedron* **1988**, *44*, 5615. For a review on organosilicon and organotin compounds in β-lactam synthesis, see: (f) Veinberg, G. A.; Lukevics, E. *Heterocycles* **1992**, *38*, 2309.

6. For general reviews on the synthesis of β-lactams and 3-amino-β-lactams respectively, see: (a) Backes, J. In *Houben-Weyl, Methoden der Organischen Chemie*; Muller, E.; Bayer, O., Eds.; Band E16B, Thieme: Stuttgart, 1991; p 31. (b) van der Steen, F. H., van Koten, G. *Tetrahedron* **1991**, *47*, 7503.

7. *The Chemistry of β-Lactams*, Page, M. I., Ed.; Chapman and Hall: London, 1992.

8. Wu, Z.; Georg, G. I.; Cathers, B. E.; Schloss, J. V. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 983.

9. Palomo, C.; Aizpurua, J. M.; Benito, A.; Galarza, R.; Khamrai, U. K.; Vazquez, J.; DePascual-Teresa, B.; Nieto, P. M.; Linden, A. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 3056.

10. (a) Palomo, C.; Aizpurua, J. M.; Legido, M.; Galarza, R.; Deya, P. M.; Dunogues, J.; Picard, J. P.; Ricci, A.; Seconi, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1239. (b) Palomo, C.; Aizpurua, J. M.; Legido, M.; Mielgo, A.; Galarza, R. *Chem. Eur. J.* **1997**, *3*, 1432.

11. This observation is general for virtually all kinds of β-lactam compounds. For some examples and leading references, see: (a) Kametani, T. *Heterocycles* **1982**, *17*, 463. (b) Bose, A. K.; Manhas, M. S.; Mathur, A.; Wagle, D. R. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Lukacs, G., Ed.; Springer: New York, 1993; Vol. 2, p 551.

12. For reviews, see: (a) Ojima, I. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1992; p 197. (b) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383.

13. Colson, P.-J.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 5918.

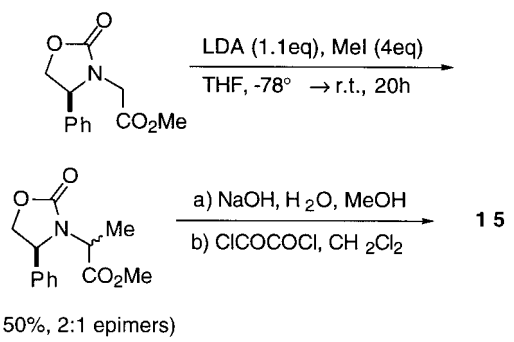
14. The imine **12** can easily be prepared by simple mixing of 33% formaldehyde aqueous solution and the readily available *C*,*C*-bis-(trimethylsilyl)methylamine. The latter can be prepared in gram quantities from commercially available *N*,*N*-dimethylcyanamide or cyanotrimethylsilane, see: (a) Picard, J. P.; Grelier, S.; Constantieux, T.; Dunoguès, J.; Aizpurua, J. M.; Palomo, C.; Petraud, M.; Barbe, B.; Lunnazi, L.; Leger, J. M. *Organometallics* **1993**, *12*, 1378, (b) Grelier, S.; Constantieux, T.; Deffieux, D.; Bordeau, M.; Dunogues, J.; Picard, J. P.; Palomo, C.; Aizpurua, J. M. *Organometallics* **1994**, *13*, 3711 and also from bis(trimethylsilyl)chloromethane, see: (c) Palomo, C.; Aizpurua, J. M.; Garcia, J. M.; Legido, M. *J. Chem. Soc; Chem. Commun.* **1991**, 524.

15. (a) Evans, D. A.; Sjögren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3783. (b) Evans, D.A.; Sjögren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3787.

16. For more detailed information on this subject, see: (a) Caperucci, A.; Ricci, A.; Seconi, G.; Dunogues, J.; Grelier, S.; Picard, J. P.; Palomo, C.; Aizpurua, J. M. *J. Organomet. Chem.* **1993**, *458*, C1. (b) Palomo, C.; Aizpurua, J. M.; Galarza, R. *Chem. Commun.* **1997**, 233. For the low temperature generation of formaldimines, see: (c) Barluenga, A. M.; Bayon, A. M.; Asensio, G. *J. Chem. Soc, Chem. Commun.* **1983**, 1109. (d) Barluenga, A. M.; Bayon, A. M.; Asensio, G. *J. Chem. Soc, Chem. Commun.* **1984**, 427.

17. Crystal data for compound **17f**: $C_{26}H_{36}N_2O_3Si_2$, M_r=480.75, tetragonal, space group *P*41, *a*=10.875(4), *c*=23.231(7) Å, *V*=2747(1) Å^{-3}, *Z*=4, D_x=1.162 g cm^{-3}, crystal dimensions: 0.16×0.20×0.48 mm, *T*=−100°C, Rigaku AFC5R diffractometer, MoKα radiation, *l*=0.71069 Å, *m*=0.157 mm^{-1}, *w*/2*q* scans, $2q_{max}$=55°, Friedel pairs for all reflections with 2*q*<40°, 6065 measured reflections of which 4661 were unique. The refinement on *F* of 442 parameters using 3828 observed reflections with *I*>2*s*(*I*) gave *R*=0.0373, *wR*=0.0329, *S*=1.615, Dr_{max}=0.26*e* Å^{-3} and an absolute structure parameter of 0.02(12). The enantiomorph was chosen using the known *S*-configuration of the benzylic stereocenter in the oxazolidine ring and was confirmed independently by the crystal-structure analysis. The crystallographic data (excluding structure factors) for structure **17f** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-113859 and can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK. [e-mail: deposit@ccdc.cam.ac.uk].

18. The acid chloride **15** was prepared according to the following sequence of reactions.



The starting methyl ester was prepared according to Evans and Sjögren, see Ref. 15.
19. Palomo, C.; Aizpurua, J. M.; Garcia, J. M.; Galarza, R.; Legido, M.; Urchegui, R.; Roman, P.; Luque, A.; Server-Carrio, J.; Linden, A. *J. Org. Chem.* **1997**, *62*, 2070.
20. For *N*-deformylation procedures, see: (a) Farina, V.; Hauck, S. I.; Walker, D. *Synlett* **1992**, 761. (b) Georg, G. I.; He, P.; Kant, J.; Wu, Z. *J. Org. Chem.* **1993**, *58*, 5771.
21. (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I. In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley–VCH: New York, 1997; p 279. (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Amino Acids* **1999**, *16*, 321.
22. For some examples on α-branched β-aminoalanine derivatives, see: (a) Hartwig, W.; Mittendorf, J. *Synthesis* **1991**, 939. (b) Seebach, D.; Studer, A.; Pfammatter, E.; Widmer, H. *Helv. Chim. Acta* **1994**, *77*, 2035. (c) Jones, R. C. F.; Crockett, A. K.; Rees, D. C.; Gilbert, I. H. *Tetrahedron Asymmetry* **1994**, *5*, 1661. (d) Gilbert, I. H.; Rees, D. C.; Crockett, A. K.; Jones, R. C. F. *Tetrahedron* **1995**, *51*, 6315. (e) Badorrey, R.; Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron Asymmetry* **1995**, *6*, 2787. (f) Obrecht, D.; Karajiannis, H.; Lehmann, C.; Schönholzer, P.; Spiegler, C.; Müller, K. *Helv. Chim. Acta* **1995**, *78*, 703. (g) Acton, J. J., III; Jones, A. B. *Tetrahedron Lett.* **1996**, *37*, 4319.
23. (a) Palomo, C.; Aizpurua, J. M.; Cuevas, C.; Mielgo, A.; Galarza, R. *Tetrahedron Lett.* **1995**, *36*, 9027. (b) Palomo, C.; Aizpurua, J. M.; Galarza, R.; Mielgo, A. *Chem. Commun.* **1996**, 633.