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A NOVEL APPROACH TO A PRECURSOR OF THE CARBAPENEM ANTIBIOTIC PS-5 *VIA* AZIRIDINE STEREOSPECIFIC CARBONYLATION

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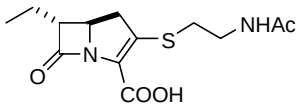
Abstract - Cobalt carbonyl-catalyzed carbonylative ring expansion of optically pure *cis*-1-benzyl-3-ethyl-2-hydroxymethylaziridine (**5**) to *trans*-β-lactam (**8**) afforded a key precursor of the carbapenem antibiotic (+)-PS5.Aziridine(**5**) was obtained in both enantiomerically pure forms by Amano PS lipase–catalyzed esterification in *n*-hexane using vinyl acetate as acyl donor. The stereochemical pathway of the carbonylation reaction was proved by configurational assignments through chemical correlation.

1. Introduction

Carbonylative ring expansion of aziridines in the presence of dicobalt octacarbonyl $Co_2(CO)_8$ as catalyst has proved a useful reaction for the stereospecific synthesis of functionalized β-lactams in excellent yields.[1,2] The reaction proceeds through nucleophilic ring opening of the aziridine by the *in situ* generated tetracarbonylcobaltate anion $[Co(CO)_4]^-$, followed by CO insertion and final ring closure to β-lactam. The reaction is stereospecific and highly regioselective: from a *cis*-aziridine *trans*-β-lactams are obtained, whereas *cis*-β-lactams are isolated from a *trans*-aziridine.[1,2]

We now wish to report that the versatility of this reaction can be applied to the synthesis of a β-lactam precursor of carbapenem antibiotic from a suitable functionalized aziridine.

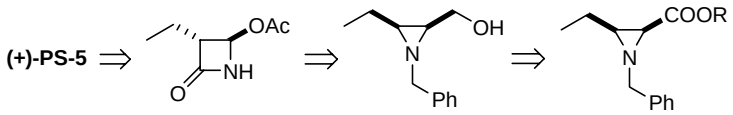
(+)-PS-5 is a natural carbapenem antibiotic isolated from cultures of *Streptomyces cremeus* and displays activity against Gram-positive and Gram-negative bacteria as well as resistance towards β-lactamases.[3] Its structural features there include the carbapenem ring system, the *trans* substitution pattern of the β-lactam



(+)-PS-5

ring and the ethyl side chain; it thus resembles the more widely known carbapenems, thienamycin and imipenem.

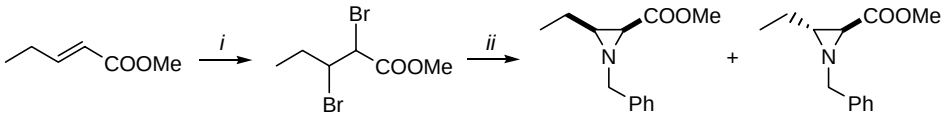
A synthetic approach[4] to (+)-PS-5 involves the construction of a β-lactam skeleton bearing an ethyl side chain in position 3 and an acetoxy group or a precursor thereof in position 4, preferably in a *trans* relationship. On the basis of our previous studies on cobalt-catalyzed carbonylation of *cis*-3-methyl-2-hydroxymethylaziridine,[1] the desired *trans*-4-acetoxy-β-lactam (**12**) was obtained by carbonylative ring expansion of a suitable substituted *cis*-aziridine, optically pure *cis*-1-benzyl-3-ethyl-2-hydroxymethylaziridine (**5**), which in turn was easily obtained from the parent aziridinecarboxylate (**3**), following the retrosynthetic pathway here reported.



12 **5** **3**

2. Results and Discussion

Synthesis of cis-*Aziridinecarboxylate (±)-**3***. – Addition of bromine to methyl *trans*-2-pentenoate (**1**), previously synthesized by Fisher esterification[5] of commercial *trans*-2-pentenoic acid gave methyl 2,3-dibromopentenoate (**2**) (97% yield). Aminative cyclization of **2** with benzylamine in methanol afforded a mixture of racemic *cis*- and *trans*-1-benzyl-3-ethyl-2-methoxycarbonylaziridines ((±)-**3**) and ((±)-**4**) in a 71:29 ratio and in 95% total yield. (Scheme 1)



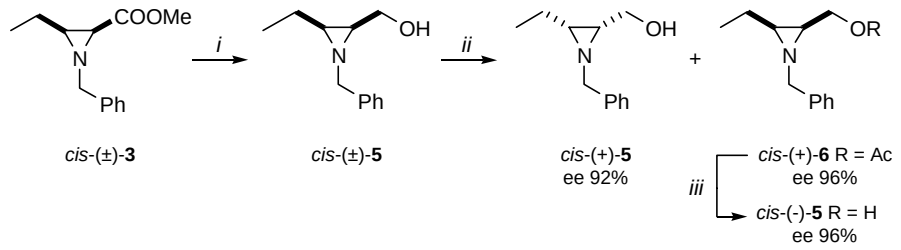
1 **2** *cis*-(±)-**3** *trans*-(±)-**4**

Scheme 1: *i.* Br_2, CCl_4 (97%); *ii.* $PhCH_2NH_2$, MeOH, rt (95%).

On the basis of ^{1}H NMR spectral analysis ($^3J_{cis} > {}^3J_{trans}$)[6] the *cis* stereochemistry was unambiguously assigned to aziridine ((±)-**3**) ($^3J_{2,3}$ 6.6 Hz) and *trans* stereochemistry to ((±)-**4**) ($^3J_{2,3}$ 2.7 Hz).

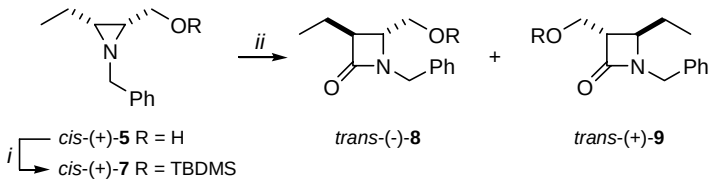
In order to obtain PS-5 in optically pure form, enantiomerically pure aziridine (**3**) should be obtained: of the several methods described in the literature[7] for the asymmetric synthesis of aziridines, enzymatic resolution is particularly suitable for aziridinecarboxylates.[8] Optical resolution of **3** in antipodes was therefore attempted by lipase-catalyzed enzymatic hydrolysis in phosphate buffer (pH 7.5) at 37 °C, following a well established protocol for aziridinecarboxylates,[8] but unfortunately all attempts failed. Since the carboxy group is known to be detrimental for the carbonylation reaction,[1] the ester function was reduced to give the corresponding aziridino alcohol. Reduction of *cis*-aziridinecarboxylate ((±)-**3**) with lithium aluminum hydride in tetrahydrofuran at room temperature thus provided *cis*-1-benzyl-3-ethyl-2-hydroxymethylaziridine ((±)- **5**) (86% yield).

Lipase-Catalyzed Resolution of Hydroxymethyl cis*-Aziridine ((±)-**5**).* – Amano PS lipase-catalyzed esterification of ((±)-**5**) in *n*-hexane at 37 °C, using vinyl acetate as acyl donor,[9] afforded optically pure (+)-**5**, ee 92% (47% yield), as well as *cis* (+)-2-acetoxymethyl-1-benzyl-3-ethylaziridine (**6**), ee 96% (50% yield) (Scheme 2). From this latter, optically pure (–)-**5**, ee 96% was obtained (98% yield) by Amano PS lipase catalyzed hydrolysis in phospate buffer.



Scheme 2: *i.* $LiAlH_4$, THF, rt (86%); *ii.* Amano PS lipase, *n*-hexane, vinyl acetate, 37 °C; *iii.* Amano PS lipase, phosphate buffer, 37 °C.

Synthesis of trans*-β-Lactam ((–)-**8**)* via *Cobalt Carbonyl-Catalyzed Carbonylation and Derivatives.* – Since the absolute configuration of both (+) and (–)-**5** was unknown, *cis*-hydroxymethylaziridine ((+)-**5**) was arbitrarily chosen for the subsequent steps of the synthesis. (+)-**5** was protected as TBDMS-ether ((+)-**7**), ee 92%, by treatment with *tert*-butyldimethylsilyl chloride and 4-dimethylaminopyridine in dichloromethane at room temperature (91% yield). Aziridine ((+)-**7**) was subsequently treated with carbon monoxide (500 psi) and $Co_2(CO)_8$ in 1,2-dimethoxyethane (DME) for 14 hours at 105 °C using a 12:1 ratio of aziridine/catalyst, to afford a 83:17 mixture of *trans*-β-lactams ((–)-**8**), ee 92%, and ((+)-**9**), ee 92%, in a 93% total isolated yield. (Scheme 3)

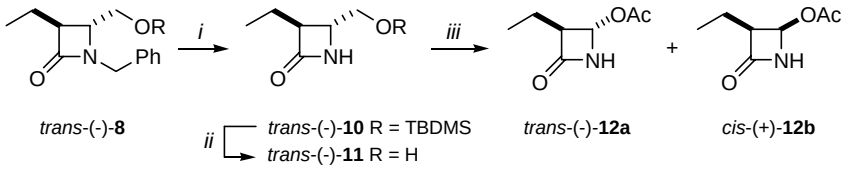


Scheme 3: *i.* TBDMSCl, DMAP, CH_2Cl_2 (91%); *ii.* $Co_2(CO)_8$, CO (500 psi), 105 °C, DME (93%).

The structures of the two β-lactam regioisomers ((–)-**8**) and ((+)-**9**) were determined by NMR and MS spectroscopies: the relative *trans* stereochemistry was unequivocally assigned on the basis of the $^3J_{3,4}$ (2.1 Hz).

trans-β-Lactam ((–)-**8**) represents a suitable precursor for the carbapenem antibiotic PS-5 through the intermediate (**12a**).[4] Debenzylation of (–)-**8** by treatment with sodium in liquid ammonia[10] at –42 °C gave *trans*-β-lactam ((–)-**10**) (63% yield) (Scheme 4). Removal of the TBDMS group by tetra *n*-butylammonium fluoride in tetrahydrofuran at room temperature[11] easily provided the 4-hydroxymethyl derivative (*trans*-(–)-**11**) in quantitative yield. Subsequent oxidation with lead tetraacetate in refluxing

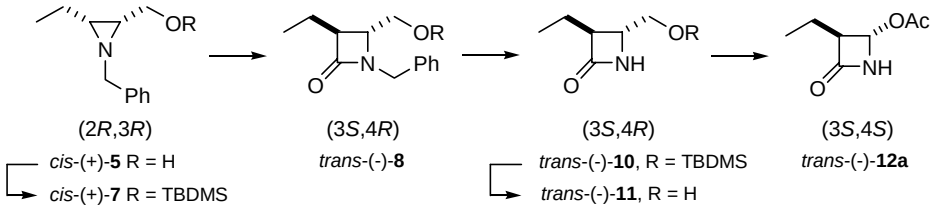
benzene in the presence of $CaCO_3$ [4,12] gave a mixture of 4-acetoxy-β-lactams (*trans*-(–)-**12a**) and (*cis*-(+)-**12b**) in a 1:1 ratio, albeit in low yields.[13]



Scheme 4: *i.* Na, liquid NH_3, –42 °C (63%); *ii.* TBAF, THF, rt (100%); *iii.* $Pb(OAc)_4$, $CaCO_3$, benzene, reflux (15%).

This lack of selectivity does not actually affect the overall result of the synthesis, for the subsequent displacement of the acetoxy group to PS-5 is reported with equilibration to the more stable *trans* configuration.[4]

Configurational Assignment: Chemical Correlation. – In order to assign the configurations of the stereocenters of (–)-**8**, the carbonylation product (*trans*-(–)-**8**) was correlated with the configurationally known *trans*-4-acetoxy-β-lactam ((–)-**12a**).[4] (Scheme 5)



Scheme 5

trans-β-Lactam ((–)-**12a**) was known to have (3*S*,4*S*) absolute configuration:[4] since oxidation does not involve the C_3 stereocenter of *trans*-(–)-**11**, we can deduce the same *S* configuration for this stereocenter. The *trans* relationship between the substituents at the C_3 and C_4 stereocenters in (–)-**11** consequently assigns the *R* configuration to the C_4 stereocenter. We can therefore infer the same (3*S*,4*R*) configuration for the stereocenters of (–)-**8**. This correlation can be extended also to the *cis*-aziridine ((+)-**5**), for which absolute configuration (2*R*,3*R*) can be deduced. In fact the carbonylation of *cis*-aziridine ((+)-**7**) to *trans*-β-lactam ((–)-**8**) does not affect the C_2 stereocenter of the aziridine which must have the same *R* configuration as the β-lactam C_4 stereocenter. The *cis* stereochemistry of aziridine ((+)-**5**) forces the C_3 stereocenter to have *R* absolute configuration. This assignment highlights the inversion of configuration at C_3 during the carbonylative ring expansion of *cis*-aziridine ((+)-**7**) to *trans*-β-lactam ((–)-**8**), which confirms the S_N2 global mechanism for the cobalt carbonyl-catalyzed carbonylation reported in the literature.[1,2] Furthermore, from the (2*R*,3*R*) absolute configuration of (+)-**5** we can infer the (3*S*,4*R*) configuration to the *trans*-β-lactam ((+)-**9**).

The configurational assignment showed that (–)-**12a** was obtained from (+)-**5**. Since the precursor of (+)-PS-5 is known[4] to be the dextrorotatory enantiomer ((+)-**12a**), the synthesis of this latter must start from

(–)-**5**, obtained as described in Scheme 5, following the same procedure.

3. Conclusions

Despite the low yield observed in the last step, the reported synthetic pathway represents a novel stereospecific approach to carbapenem antibiotic PS-5 *via* cobalt carbonyl-catalyzed carbonylative ring expansion of a suitable functionalized optically pure *cis*-aziridine. The carbonylation reaction, *i.e.* the key step of the whole synthesis, proved stereospecific, highly regioselective and afforded excellent yield.

Moreover, correlation of *trans*-β-lactam ((–)-**8**) with the configurationally known *trans*-4-acetoxy β-lactam ((–)-**12a**) allowed us the configurational assignments to the stereocenters of the synthesized *trans*-β-lactams ((–)-**8**, (+)-**9**, (–)-**10** and (–)-**11**) and of *cis*-aziridines ((+)-**5**, (+)-**6** and (+)-**7**).

EXPERIMENTAL

The instrumentation has already been described.[8] ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on 200 MHz and 400 MHz spectrometers. Chemical shifts are reported in δ values from TMS as internal standard. Coupling constants (*J*) are given in Hz. All organic solvents were dried and distilled by standard methods prior to use and all reactions were carried out using oven-dried glassware. Chromatographic purification of compounds was performed on silica gel (ϕ 0.05-0.20 mm). The metal catalyst $Co_2(CO)_8$ was purchased from Merck; *trans*-2-pentenoic acid was purchased from Aldrich. The enzyme Amano PS lipase was generously gifted by Amano Pharmaceutical Company, Ltd. (Nagoya, Japan) and used without further purification.

The assignments of the observed NMR (^{1}H, ^{13}C) resonances of (–)-**8** and (+)-**9** were carried out using 2D-heteronuclear correlated spectroscopy (H,C-COSY).[14] Enantiomeric excesses (ee's) were determined by the analysis of the ^{1}H NMR spectra recorded in $CDCl_3$ in the presence of a 1.5- to 3-fold excess of the chiral solvating agent (*R*)-(–)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Ega Chemie). The ee of aziridino alcohol ((+)-**5**) was evaluated after its conversion into the corresponding (–)-**6** acetoxy derivative by treatment with acetyl chloride in dichloromethane at 0 °C in the presence of triethylamine. The determination of ee's is accurate to ±5%.[15]

Methyl* trans-*2-Pentenoate (**1**)[5] – Esterification of commercial *trans*-2-pentenoic acid was carried out according to the literature procedure. ^{1}H NMR (200 MHz): δ 1.70 (3H, t, *J* 7.4), 2.23 (2H, ddq, *J* 1.7, 6.4, 7.4), 3.72 (3H, s), 5.82 (1H, dt, *J* 15.7, 1.7), 7.02 (1H, dt, *J* 15.7, 6.4). MS *m/z*: 114 (M^+), 99, 83 (base peak), 82, 72, 71, 59, 55.

Methyl 2,3-Dibromopentanoate (**2**)[16] **–** Bromine (1.28 mL, 24.92 mmol) was added dropwise at rt to a

stirred solution of **1** (2.81 g, 24.68 mmol) in carbon tetrachloride (120 mL). The reaction mixture was gently refluxed for 2 h until decoloration: the solution was then cooled and evaporated *in vacuo* to afford methyl 2,3-dibromopentenoate (**2**) (6.54 g, 97 %) as an orange liquid which was used without further purification. ^{1}H NMR (200 MHz): δ 1.10 (3H, t, *J* 7.2), 1.91 (1H, m), 2.32 (1H, m), 3.83 (3H, s), 4.32-4.73 (2H, m). MS *m/z*: 277-275-273 [$(M+1)^+$], 276-274-272 (M^+), 245-243-241, 217-215-213, 195-193, 163-161, 135-133, 113 (base peak), 81, 59, 55.

cis-*(±)-1-Benzyl-3-ethyl-2-methoxycarbonylaziridine* (**3**) *and* **trans-*(±)-1-benzyl-3-ethyl-2-methoxycarbonylaziridine*** (**4**) **–** A solution of methyl 2,3-dibromopentanoate (**2**) (7.65 g, 27.94 mmol) in methanol (70 mL) was slowly added at 0 °C to a stirred solution of benzylamine (12.6 mL, 115.35 mmol) in methanol (200 mL). The reaction mixture was stirred overnight and allowed to warm to rt. After rotary evaporation of the solvent, the residue was dissolved in ether (180 mL), washed with water (360 mL) and the aqueous phase extracted with ether (3×90 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to give a crude brown-yellowish oil which was chromatographed (light petroleum/ether 80:20 and then 60:40) to afford the *cis*-aziridine (**3**) (4.02 g) and the *trans*-aziridine (**4**) (1.81 g) as yellowish oils in a 69:31 ratio and in 95% total yield. *cis*-Aziridine (**3**) was further purified by *in vacuo* distillation on a Vigreux column: colourless oil, bp 102 °C (0.6 mmHg). ^{1}H NMR spectroscopy showed compound *trans*-**4** as a 72:28 mixture of two invertomers at nitrogen, due to slow nitrogen inversion on the NMR scale.

cis-(±)-(**3**): ^{1}H NMR (200 MHz): δ 0.88 (3H, t, *J* 7.4), 1.39-1.77 (2H, m), 1.87 (1H, q, *J* 6.6), 2.26 (1H, d, *J* 6.6), 3.53 (1H, d, *J* 13.5), 3.62 (1H, d, *J* 13.5), 3.72 (3H, s), 7.22-7.36 (5H, m). MS *m/z*: 219 (M^+), 204, 190, 160, 146, 131, 128, 91 (base peak), 68, 65. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.20; H, 7.83; N, 6.39.

trans-(±)-(**4**): ^{1}H NMR (400 MHz): major invertomer: δ 0.87 (3H, t, *J* 7.4), 1.38-1.59 (2H, m), 2.27 (1H, dt, *J* 2.7, 5.9), 2.51 (1H, d, *J* 2.7), 3.69 (3H, s), 3.91 (1H, d, *J* 13.5), 3.99 (1H, d, *J* 13.5), 7.29-7.41 (5H, m); minor invertomer: δ 1.09 (3H, t, *J* 7.3), 1.59-1.83 (2H, m), 2.05 (1H, m), 2.49 (1H, m), 3.72 (3H, s), 3.65 (1H, d, *J* 13.8), 3.92 (1H, d, *J* 13.8), 7.22-7.29 (5H, m). MS *m/z*: 219 (M^+), 204, 190, 160, 146, 131, 128, 91 (base peak), 68, 65. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.24; H, 7.84; N, 6.36.

cis-*(±)-1-Benzyl-3-ethyl-2-hydroxymethylaziridine* (**5**) **–** 1.0 M $LiAlH_4$ solution in THF (13.7 mL) was slowly added dropwise through a dropping funnel to a stirred solution of *cis*-aziridine ((±)-**3**) (1.5 g, 6.85 mmol) in freshly distilled anhydrous THF (14 mL) at rt. After 40 min TLC (ether/light petroleum 80:20) showed total disappearance of the starting material: the reaction mixture was then cooled to 0 °C and

carefully quenched by dropwise addition of 0.67 mL of water, followed by 0.67 mL of a 0.15 N NaOH solution. The white inorganic precipitate was filtered off and washed with abundant ether (150 mL): the filtrate was dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Chromatography on silica gel (ether/light petroleum 80:20 and finally pure ether) gave *cis*-(±)-**5** as a light pink sticky oil (1.12 g, 86%). ^{1}H NMR (200 MHz): δ 0.88 (3H, t, *J* 7.3), 1.42 (2H, m), 1.62 (1H, q, *J* 6.6), 1.84 (1H, dt, *J* 5.0, 6.6), 2.38 (1H, br), 3.45 (1H, d, *J* 13.1), 3.48 (1H, dd, *J* 11.4, 6.8), 3.55 (1H, d, *J* 13.1), 3.71 (1H, dd, *J* 11.4, 5.0), 7.22-7.36 (5H, m). MS *m/z*: 190 ([M–1]$^+$), 160, 146, 117, 100, 91, 72 (base peak), 65. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.33; H, 8.98; N, 7.33.

Lipase-Catalyzed Resolution of* cis-*(±)-1-Benzyl-3-ethyl-2-hydroxymethylaziridine (**5**) **–** Amano PS Lipase (657 mg) was added to a mechanically stirred solution of *cis*-aziridine ((±)-**5**) (1.31 g, 6.88 mmol) in *n*-hexane (65 mL) in a double-necked round bottom flask placed in a thermostatic bath at 37 °C. Vinyl acetate (3.2 mL, 34.72 mmol) was then added: after 35 min the reaction mixture was filtered to remove the enzyme and concentrated *in vacuo*. Chromatography (ether/light petroleum 70:30) afforded unreacted *cis*-(2*R*,3*R*)-(+)-1-benzyl-3-ethyl-2-hydroxymethylaziridine (**5**) (620 mg, 47%), which was further purified by *in vacuo* distillation (colorless viscous oil, bp 150 °C/4×10^{-5} mbar), $[\alpha]_D$ +29.4° (*c* 1.4, MeOH), ee 92%, and *cis*-(2*S*,3*S*)-(+)-2-acetoxymethyl-1-benzyl-3-ethylaziridine (**6**) (797 mg, 50%), $[\alpha]_D$ +15.1° (*c* 2.7, $CHCl_3$), ee 96%. ^{1}H NMR (200 MHz): δ 0.96 (3H, t, *J* 7.3), 1.39-1.64 (3H, m), 1.64 (1H, q, *J* 6.6), 1.89 (1H, dt, *J* 7.3, 6.1), 2.01 (3H, s), 3.46 (1H, d, *J* 13.2), 3.60 (1H, d, *J* 13.2), 4.06 (1H, dd, *J* 7.3, 11.7), 4.19 (1H, dd, *J* 5.7, 11.7), 7.23-7.40 (5H, m). MS *m/z*: 174 ([M–59]$^+$), 160, 142, 100, 91, 72, 65, 43 (base peak). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.10; H, 8.18; N, 5.97.
Optically pure *cis*-(2*S*,3*S*)-(–)-**5** was obtained as follows: Amano PS lipase (50 mg) was added to a suspension of *cis*-(2*S*,3*S*)-(+)- **6**, ee 96% (500 mg) in phosphate buffer (pH 7.5, 0.1 M, 25 mL) and stirred at 37 °C for 20 h. The reaction mixture was extracted with ethyl acetate (4×20 mL); the combined organic phases were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$ and evaporated. Chromatography on silica gel (light petroleum/ether 70:30) gave *cis*-(2*S*,3*S*)-(–)-**5** (396 mg, 98% yield), $[\alpha]_D$ –30.5° (*c* 1.6, MeOH), ee 96%.

cis-*(2R,3R)-(+)-1-Benzyl-2-(*tert-*butyldimethylsilyloxy)methyl-3-ethylaziridine* (**7**) **–** *cis*-Aziridine ((+)-**5**), ee 92% (322 mg, 1.69 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL): DMAP (515 mg, 4.22 mmol) and TBDMSCl (305 mg, 2.02 mmol) were added at rt under magnetic stirring and nitrogen atmosphere. After 40 min the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with water (2×20 mL) and brine (20 mL), dried over $MgSO_4$ and rotary evaporated. Chromatography on silica gel (light petroleum/ether 90:10) gave *cis*-(+)-**7** as a light yellow oil (468 mg, 91%), $[\alpha]_D$ +14.0° (*c* 2.3,

$CHCl_3$), ee 92%. ^{1}H NMR (200 MHz): δ 0.094 (6H, s), 0.94 (9H, s), 0.96 (3H, t, *J* 7.1), 1.29-1.63 (3H, m), 1.81 (1H, q, *J* 6.2), 3.48 (1H, d, *J* 13.4), 3.59 (1H, d, *J* 13.4), 3.62 (1H, dd, *J* 6.5, 10.9), 3.81 (1H, dd, *J* 5.8, 10.9), 7.24-7.42 (5H, m). MS *m/z*: 305 (M^+), 290, 276, 248, 214, 206, 174, 160, 158, 91 (base peak), 75, 73. Anal. Calcd for $C_{18}H_{31}NOSi$: C, 70.76; H, 10.23; N, 4.58. Found: C, 70.86; H, 10.25; N, 4.57.

trans-*(3S,4R)-(–)-1-Benzyl-4-(*tert*-butyldimethylsilyloxy)methyl-3-ethylazetidin-2-one* (**8**) *and* **trans-*(3S,4R)-(–)-1-benzyl-3-(*tert*-butyldimethylsilyloxy)methyl-4-ethylazetidin-2-one*** (**9**) **–** In a 45-mL stainless steel autoclave equipped with a glass liner and a stirring bar, *cis*-aziridine ((+)-**7**) (395 mg, 1.29 mmol) was dissolved in freshly distilled anhydrous and O_2 free DME (10 mL) and $Co_2(CO)_8$ (38 mg, 0.11 mmol) was added. After purging four times with 300 psi CO, the autoclave was charged with 500 psi CO and kept in an oil bath for 14 h at 105 °C. The autoclave was then opened and ether was added to the brown clear solution to decompose the catalyst. After 1 h, the reaction mixture was filtered through a small silica gel column, washed with abundant ether and concentrated *in vacuo*. Chromatography on silica gel (light petroleum/ether 70:30) afforded, as light yellow oils, the two β-lactams regioisomers *trans*-(3*S*,4*R*)-(–)-**8** (323 mg), $[\alpha]_D$ –44.4° (*c* 1.6, $CHCl_3$), ee 92% and *trans*-(3*S*,4*R*)-(+)-**9** (77 mg), $[\alpha]_D$ +22.3° (*c* 1.1, $CHCl_3$), ee 92% in a 83:17 ratio and in 93% total isolated yield (carbonylation of racemic (±)-**7** proceeded instead with 99% yield).

trans-(3*S*,4*R*)-(–)-**8**: ^{1}H NMR (400 MHz): δ 0.035 (6H, s, ^{t}Bu$\underline{Me}_2$Si–), 0.89 (9H, s, $^t\underline{Bu}Me_2$Si–), 0.97 (3H, t, *J* 7.4, C$\underline{H}_3$CH$_2$–), 1.60 (1H, ddq, *J* 8.8, 13.9, 7.4, CH$_3$C$\underline{H}_2$–), 1.79 (1H, ddq, *J* 5.7, 13.9, 7.4, CH$_3$C$\underline{H}_2$–), 2.84 (1H, dddd, *J* 0.7, 2.1, 5.7, 8.8, CH$_3$CH$_2$C$\underline{H}$–), 3.24 (1H, ddd, *J* 2.1, 4.3, 5.4, –C$\underline{H}$CH$_2$O–), 3.65 (1H, dd, *J* 5.4, 10.8, –C$\underline{H}_2$O–), 3.69 (1H, dd, *J* 4.3, 10.8, –C$\underline{H}_2$O–), 4.09 (1H, d, *J* 15.0, –C$\underline{H}_2$Ph), 4.70 (1H, d, *J* 15.0, –C$\underline{H}_2$Ph), 7.25-7.36 (5H, m, aromatic). ^{13}C NMR: δ –4.86 (^{t}Bu$\underline{Me}_2$Si–), –4.84 (^{t}Bu$\underline{Me}_2$Si–), 12.3 (C$\underline{H}_3$CH$_2$–), 18.9 (Me$_3\underline{C}$Me$_2$Si–), 21.9 (CH$_3\underline{C}$H$_2$–), 26.5 ($\underline{Me}_3$CMe$_2$Si–), 45.5 (–$\underline{C}$H$_2$Ph), 54.5 (CH$_3$CH$_2\underline{C}$H–), 58.8 (–$\underline{C}$HCH$_2$O–), 64.4 (–$\underline{C}$H$_2$O–), 128.2, 128.9, 129.3, 137.2, 170.8 (carbonyl). MS *m/z*: 333 (M^+), 332, 318, 305, 288, 276, 248, 207, 206 (base peak), 188, 143, 91, 75, 73. Anal. Calcd for $C_{19}H_{31}NO_2Si$: C, 68.42; H, 9.37; N, 4.20. Found: C, 68.50; H, 9.35; N, 4.18.

trans-(3*S*,4*R*)-(+)-**9**: ^{1}H NMR (400 MHz): δ 0.058 (6H, s, ^{t}Bu$\underline{Me}_2$Si–), 0.87 (3H, t, *J* 7.5, –CH$_2$C$\underline{H}_3$), 0.88 (9H, s, $^t\underline{Bu}Me_2$Si–), 1.34-1.46 (1H, m, –C$\underline{H}_2$CH$_3$), 1.66-1.84 (1H, m, –C$\underline{H}_2$CH$_3$), 2.92 (1H, dddd, *J* 0.6, 2.1, 3.7, 5.8, –OCH$_2$C$\underline{H}$–), 3.42 (1H, ddd, *J* 2.1, 4.1, 8.9, –C$\underline{H}$CH$_2$CH$_3$), 3.87 (1H, dd, *J* 3.7, 10.8, –OC$\underline{H}_2$–), 3.91 (1H, dd, *J* 5.8, 10.8, –OC$\underline{H}_2$–), 4.10 (1H, d, *J* 15.4, –C$\underline{H}_2$Ph), 4.65 (1H, d, *J* 15.4, –C$\underline{H}_2$Ph), 7.25-7.35 (5H, m, aromatic). ^{13}C NMR: δ –4.8 (^{t}Bu$\underline{Me}_2$Si–), –4.7 (^{t}Bu$\underline{Me}_2$Si–), 10.3 (–CH$_2\underline{C}$H$_3$), 19.0 (Me$_3\underline{C}$Me$_2$Si–), 25.7 (–$\underline{C}$H$_2$CH$_3$), 26.5 ($\underline{Me}_3$CMe$_2$Si–), 44.4 (–$\underline{C}$H$_2$Ph), 57.2 (–$\underline{C}$H CH$_2$CH$_3$), 58.5 (–OCH$_2\underline{C}$H–), 60.6 (–O$\underline{C}$H$_2$–), 128.2, 128.8, 129.3, 136.8, 168.4 (carbonyl). MS *m/z*: 334 [$(M+1)^+$], 333,

332, 318, 304, 277, 276 (base peak), 246, 219, 184, 143, 129, 91, 75, 73. Anal. Calcd for $C_{19}H_{31}NO_2Si$: C, 68.42; H, 9.37; N, 4.20. Found: C, 68.53; H, 9.39; N, 4.17.

trans-*(3S,4R)-(–)-4-(*tert-*Butyldimethylsilyloxy)methyl-3-ethylazetidin-2-one* (**10**) – Sodium (131 mg, 5.70 mmol) was dissolved in liquid ammonia (12 mL) in a 50 mL schlenk tube cooled at – 42 °C and a solution of *trans*-(–)-**8** ee 92% (602 mg, 1.81 mmol) in anhydrous THF (4 mL) was added dropwise *via* syringe under vigorous stirring. After 5 min the reaction mixture was quenched by adding solid ammonium chloride until disappearance of the dark blue color. Liquid ammonia was left to evaporate, thus obtaining a lemon-yellow solution which was filtered to remove solid NaCl and washed with abundant ether. After rotary evaporation, the crude sticky light yellow oil was chromatographed (ether/light petroleum 50:50) to afford *trans*-(–)-**10** (275 mg, 63%) as a colorless viscous liquid, $[\alpha]_D$ – 25.6° (*c* 1.2, $CHCl_3$). ^{1}H NMR (200 MHz): δ 0.070 (6H, s), 0.90 (9H, s), 1.02 (3H, t, *J* 7.4), 1.59-1.90 (2H, m), 2.79 (1H, dddd, *J* 1.4, 2.2, 6.1, 8.5), 3.41 (1H, ddd, *J* 2.2, 4.7, 6.5), 3.64 (1H, dd, *J* 6.5, 10.5), 3.76 (1H, dd, *J* 4.7, 10.5), 5.93 (1H, br). MS *m/z*: 243 (M^+), 228, 200, 186, 158, 143, 116 (base peak), 98. Anal. Calcd for $C_{12}H_{25}NO_2Si$: C, 59.21; H, 10.35; N, 5.75. Found: C, 59.25; H, 10.34; N, 5.77.

trans-*(3S,4R)-(–)-3-Ethyl-4-hydroxymethylazetidin-2-one* (**11**) – Tetrabutylammonium fluoride (345 mg, 1.322 mmol) was dissolved in dry THF (1 mL) and added dropwise at rt under nitrogen flow to a stirred solution of *trans*-(–)-**10** (268 mg, 1.103 mmol) in THF (5 mL). After 30 min the reaction mixture was rotary evaporated and the crude residue purified by chromatography on silica gel (ether/light petroleum/MeOH 82:9:9) to give *trans*-(–)-**11** as a colorless sticky oil (142 mg, 100%), $[\alpha]_D$ –44.7° (*c* 1.2, $CHCl_3$). ^{1}H NMR (200 MHz): δ 1.01 (3H, t, *J* 7.4), 1.56-1.91 (2H, m), 2.86 (1H, dddd, *J* 1.3, 2.0, 6.2, 8.4), 3.47 (1H, m), 3.62 (2H, m), 3.82 (1H, m), 6.82 (1H, br). MS *m/z*: 130 [$(M+1)^+$], 98, 86, 70, 68, 57 (base peak), 55. Anal. Calcd for $C_6H_{11}NO_2$: C, 55.8; H, 8.58; N, 10.84. Found: C, 55.75; H, 8.60; N, 10.87.

trans-*(3S,4S)-(–)-4-Acetoxy-3-ethyl-azetidin-2-one* (**12a**) *and* **cis-*(+)-4-acetoxy-3-ethylazetidin-2-one*** (**12b**)[4,12] **–** Lead tetraacetate (749 mg, 1.69 mmol) and calcium carbonate (169 mg, 1.69 mmol) were added to 5 mL of anhydrous benzene and the mixture was refluxed for 15 min. A solution of *trans* (–)-**11** (109 mg, 0.84 mmol) in benzene (5 mL) was added dropwise. After refluxing for 4 h, the mixture was filtered, washed with abundant ether and rotary evaporated to give a brown residue which was dissolved in water (20 mL) and extracted with ether (3×15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (ether/light petroleum 50:50) gave *trans*-4-acetoxy derivative ((3*S*,4*S*)-(–)-**12a**) (10 mg), $[\alpha]_D$ –96.9° (*c* 0.95, $CHCl_3$) [lit.,[4] (3*R*,4*R*) $[\alpha]_D$ +100° ($CHCl_3$)] and

cis-4-acetoxy derivative ((–)-**12b**) (10 mg), $[\alpha]_D$ +18.5° (*c* 0.95, $CDCl_3$), both as a colorless liquid, in a total 15% isolated yield.

trans-(3*S*,4*S*)-(–)-**12a**: ^{1}H NMR (200 MHz): δ 1.06 (3H, t, *J* 7.4), 1.63-1.92 (2H, m), 2.12 (3H, s), 3.17 (1H, ddd, *J* 1.1, 6.7, 7.8), 5.54 (1H, d, *J* 1.1), 6.46 (1H, br). MS *m/z*: 158 [$(M+1)^+$], 114, 98, 72, 70, 57 (base peak), 55.

cis-(+)-**12b**: ^{1}H NMR (200 MHz): δ 1.07 (3H, t, *J* 7.4), 1.68-1.85 (2H, m), 2.13 (3H, s), 3.28 (1H, m), 5.87 (1H, d, *J* 4.3), 6.43 (1H, br). MS *m/z*: 158 [$(M+1)^+$], 114, 98, 72, 70, 57 (base peak), 55.

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