Pergamon

Bioorganic & Medicinal Chemistry 10 (2002) 1813–1818

BIOORGANIC & MEDICINAL CHEMISTRY

Efficient and Highly Stereoselective Synthesis of a β-Lactam Inhibitor of the Serine Protease Prostate-Specific Antigen

Rita Annunziata, Maurizio Benaglia,* Mauro Cinquini, Franco Cozzi and Alessandra Puglisi

Centro CNR and Dipartimento di Chimica Organica e Industriale, Universita' degli Studi di Milano, Via Golgi 19, I-20133 Milan, Italy

Received 4 October 2001; accepted 8 January 2002

Abstract—An efficient synthesis of a β-lactam precursor of the serine protease, prostate-specific antigen inhibitor **1** has been accomplished. The synthesis relies on two completely stereoselective reactions that allow the introduction of the stereocenters at C-3 and C-4 of the azetidinone ring in a predictable manner. © 2002 Elsevier Science Ltd. All rights reserved.

Introduction

The recognized ability of a variety of monocyclic β-lactams to inhibit proteases[1] led to the design of compound **1** (Fig. 1) as a powerful inhibitor of the serine protease, prostate-specific antigen (PSA),[2] a widely used marker for prostate carcinoma.[3] The recently discovered involvement of PSA in some degenerative processes implicated in the development of prostate and breast tumors[4] makes β-lactam **1** and analogues important synthetic targets.

Compound **1** has been synthesized in racemic (10 steps, 9.1% overall yield from 4-hydroxy hydrocinnamic acid) and enantiopure form [14 steps, 0.9% overall yield from (*S*)-aspartic acid].[2] Here we report a new synthesis of enantiopure **2** (Fig. 1), a known advanced precursor of **1**, that is based on a protocol for the preparation of β-lactams developed in our laboratories over the last few years. This methodology[5] involves the stereoselective condensation between the titanium enolate of a 2-pyridylthioester and an imine as the azetidinone ring forming step.

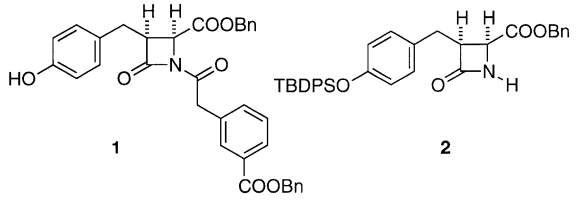


Figure 1. Structure of PSA inhibitor **1** and precursor **2**.

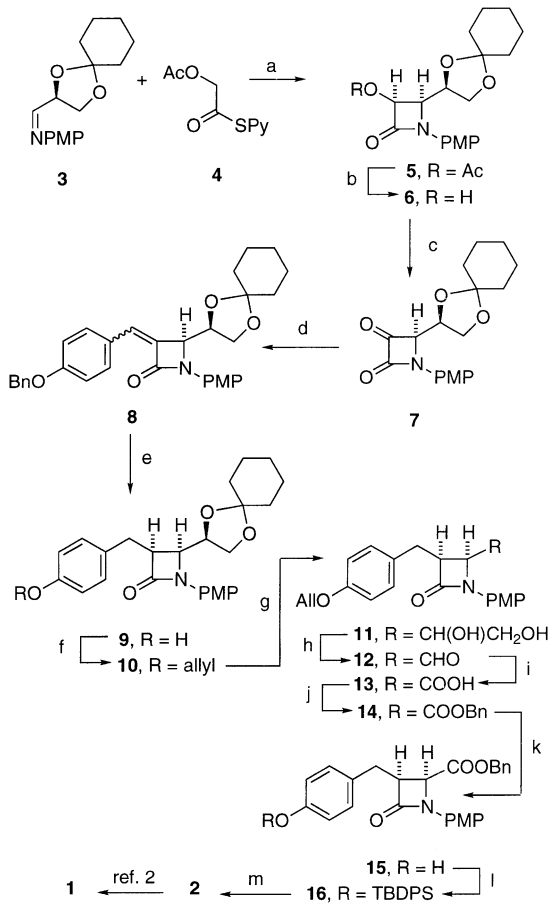
Results and Discussion

In planning the synthesis of **2**, α,β-dialkoxyimine (*R*)-**3** was selected to introduce the β-lactam's nitrogen and C-4 atoms, and the carboxy function at C-4 in the target molecule [via deprotection of the diol function in (*R*)-**3** and its oxidative degradation]. Moreover, on the basis of the known stereochemical preference of our β-lactam synthesis,[5] it was anticipated that the use of (*R*)-**3** would allow the generation of the C-4 stereocenter in the correct configuration and in a highly stereoselective fashion.

Also the introduction of the benzylic substituent at C-3 in a *cis* position to the carboxy group at C-4 required some synthetic planning. Since it was expected that the use of a 2-pyridylthioester derived from 4-hydroxy hydrocinnamic acid would mainly lead to a 3,4-*trans* azetidinone,[5,6] it was decided to stereoselectively introduce the side chain at C-3 exploiting the previously established stereocenter at C-4 (see above). Therefore, 2-pyridylthio acetoxyacetate **4**[5] was selected as the enolate partner of the condensation. Deprotection of the hydroxy group followed by oxidation to the ketone

*Corresponding author. Tel.: +39-02-5031-4171; fax: +39-02-5031-4159; e-mail: maurizio.benaglia@unimi.it

0968-0896/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0968-0896(02)00017-2



Scheme 1. Stereoselective multistep synthesis of compound **2.** Abbreviations: Py = 2-pyridyl; PMP: 4-MeOPh; All: $CH_2=CH-CH_2$-; TBPDS: *t*-$BuPh_2Si$. Reagents: (a) $TiCl_4$, Et_3N; (b) KOH; (c) P_2O_5, DMSO; (d) 4-$BnOPhCH_2PPh_3Br$, BuLi; (e), H_2, 10% Pd/C; (f) AllBr, K_2CO_3; (g) TFA, H_2O; (h) $NaIO_4$; (i) Jones reagent; (j) BnBr, K_2CO_3; (k) $PdOAc_2$, PPh_3; then wet SiO_2; (l) TBDPSCl, imidazole; (m) $Ce(NH_4)_2(NO_3)_6$.

would provide the required scenario for 3,4-*cis* stereoselective alkylation at C-3 via olefination and double bond reduction.

Condensation[5b] of the titanium enolate derived from 2-pyridylthio acetoxyacetate **4** with the *N*-4-methoxyphenylimine of (*S*)-*O,O*-cyclohexylidene protected glyceraldehyde **3**[7] gave β-lactam (3*S*,4*R*,4′*R*)-**5** as a single product in 65% isolated yield (Scheme 1). The stereoisomeric purity of this compound was determined by 300 MHz ^{1}H NMR spectroscopy on the crude reaction product. Ester hydrolysis (1 N aqueous KOH, THF/MeOH 9:1) gave the 3-hydroxy substituted β-lactam **6** in 94% yield. Alternatively, this compound was conveniently prepared in a one-pot procedure carrying out the hydrolysis on the crude β-lactam. This protocol afforded compound **6** in 72% over the two steps. The 3-hydroxysubstituted azetidinone thus obtained was oxidized following a modification of Palomo's procedure[8] to ketone **7** (85% yield), which was then converted into alkene **8** in 73% yield by standard Wittig chemistry (4-benzyloxybenzyl triphenylphosphonium bromide, BuLi, THF, −20 °C). The 93:7 mixture of isomeric alkenes was then catalytically reduced (H_2, cat 10% Pd/C, EtOH) to exclusively afford the 3,4-*cis* configurated compound **9** in 98% yield. Hydroxy group protection as the allyl ether (allyl bromide, K_2CO_3, CH_3CN, 50 °C) gave crude compound **10**, which was then subjected to ketal hydrolysis (TFA, H_2O, 0 °C to rt). Oxidative degradation of the crude diol **11** ($NaIO_4$, H_2O, AcOEt, RT) gave the aldehyde **12** that was isolated in 73% overall yield from **9**.[9] Oxidation to the crude acid **13** (Jones' reagent, acetone, H_2O, rt), followed by esterification (K_2CO_3, benzyl bromide, refluxing acetone) gave compound **14** in 68% overall yield from **12**.

At this stage, conversion of **14** into target **1** merely required removal of the 4-methoxyphenyl group, introduction of the side chain at nitrogen, and phenol deprotection. To asses the feasibility of this approach, nitrogen deprotection with CAN under Georg's conditions[10] was attempted on a model compound featuring an ethoxycarbonyl instead of the benzyloxycarbonyl group at C-4 of **14**. This reaction occurred in 70% yield without affecting the allyl protection at the phenol oxygen. For correlative purposes, however, compound **14** was first transformed (cat. $Pd(OAc)_2$, PPh_3, refluxing EtOH; then wet SiO_2, rt) into crude phenol **15**, which was then protected as its TBDPS ether **16** under standard conditions (TBDPSCl, imidazole, DCM). Compound **16**, obtained in 51% overall yield from **14**, was finally converted into β-lactam **2** by CAN degradation (CAN, CH_3CN, H_2O, −20 °C, 70% yield), completing the formal total synthesis of **1**. Compound **2** was thus obtained from **3** in 6.7% overall yield over 13 steps.

The success of this synthetic strategy relied on two completely stereoselective transformations: the synthesis of β-lactam **5** and the reduction of alkene **8**. Both of these reactions deserve some comments. The formation of the 3,4-*cis*-4,4′-*syn* azetidinone **5** was expected on the basis of a model of stereoselection proposed in the course of previous studies.[11] This rationale involves addition of the (*E*)-enolate of **4** (CIP rules)[12] on the less hindered diastereoface of the α-chelated (*E*)-imine **3** in a cyclic transition structure (**A**, Fig. 2). The highly stereoselective reduction of the double bond in compound **8** can be explained simply on the basis of hydrogen addition from the side of the small substituent at C-4 (the H atom) as in **B** (Fig. 2). This sort of rationalization has ubiquitously been invoked to account for many stereoselective transformations involving a trigonal C atom at position 3 of a β-lactam ring and occurring under the influence of a stereocenter at C-4.[13]

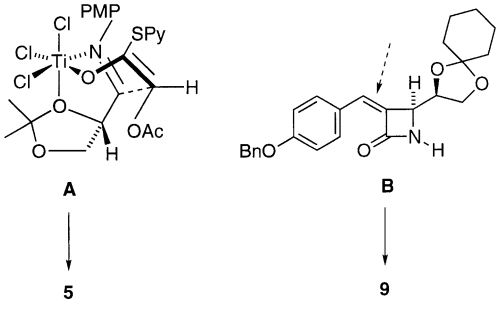


Figure 2. Models of stereoselection **A** and **B** explaining the stereoselective formation of **5** and **9**.

Conclusion

In conclusion, an efficient synthesis of a precursor of the serine protease, prostate specific antigen inhibitor **1** has been accomplished. The synthesis relies on two completely stereoselective reactions that allow the introduction of the stereocenters at C-3 and C-4 in a predictable manner. It is also worth mentioning that the employed reaction sequence can tolerate the introduction of points of structural diversity at C-3, C-4 and N-1, thus opening access to differently substituted compounds of potentially stronger inhibiting capacity. From a more general point of view, this work shows how even largely speculative rationalizations of the course of a stereoselective reaction can prove to be a useful predictive tool in designing an effective synthetic strategy.

Experimental

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on $CDCl_3$ solutions at 300 and 75 MHz, respectively. Resonances are in ppm downfield from TMS; coupling constants are in Hz. FTIR spectra were recorded on pure liquids or Nujol film. Optical rotations were measured on DCM solutions. Thioester **4**[5b] and 4-benzyloxybenzyl triphenylphosphonium bromide[14] were known compounds, that were prepared according to the literature procedures. Imine **3** was prepared from the corresponding aldehyde[7] as described for its enantiomer.[5b]

(3*S*,4*R*,4′*R*)-1-(4-Methoxyphenyl)-3-acetoxy-4-(1,4-dioxaspiro[4.5]dec-2-yl)azetidin-2-one 5. To a stirred solution of thioester **4** (2.11 g, 10 mmol) in anhydrous DCM (30 mL) cooled at −78 °C and kept under nitrogen, $TiCl_4$ (11 mL of a 1 M solution in DCM, 11 mmol) was added dropwise. Triethylamine (1.7 mL, 12 mmol) was then added dropwise, and the resulting dark purple solution was stirred at −78 °C for 20 min. Imine **3** (1.38 g, 5 mmol) dissolved in DCM (20 mL) was then added dropwise, and the resulting mixture was stirred at −78 °C for 6 h and then allowed to slowly warm-up to rt. After stirring overnight, the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ and the mixture was filtered through a Celite cake. The organic layer was separated, and the aqueous layer was extracted with 3×25 mL of DCM. The combined organic layers were dried over Na_2SO_4, the solvent was evaporated under vacuum, and the crude residue was purified by flash chromatography with a 60:40 hexanes/ethylacetate mixture as eluant. The product (1.22 g) was obtained in 65% yield as a pale yellow solid, mp 101–103 °C. IR: 1765, 1760 cm^{-1}. $[\alpha]_D^{23}$ −50.3 (*c* 0.32). ^{1}H NMR: δ 7.70 (B part of an AB system, *J* = 8.3 Hz, 2H), 6.89 (A part of an AB system, *J* = 8.3 Hz, 2H), 6.03 (d, *J* = 5.1 Hz, 1H), 4.37 (dt, *J* = 6.4, 8.7 Hz, 1H), 4.31 (dd, *J* = 5.1, 8.7 Hz, 1H), 4.08 (dd, *J* = 6.4, 8.8 Hz, 1H), 3.81 (s, 3H), 3.64 (dd, *J* = 6.4, 8.8 Hz, 1H), 2.18 (s, 3H), 1.73–1.33 (m, 10H). ^{13}C NMR: δ 169.0, 167.0, 156.0, 131.1, 119.0, 113.9, 110.9, 76.2, 73.0, 66.0, 61.9, 55.5, 36.3, 34.4, 25.0, 24.0, 23.8, 20.5. $C_{20}H_{25}NO_6$ requires: C, 63.99; H, 6.71; N, 3.73. Found: C, 64.13; H, 6.56; N, 3. 64.

(3*S*,4*R*,4′*R*)-1-(4-Methoxyphenyl)-3-hydroxy-4-(1,4-dioxaspiro[4.5]dec-2-yl)azetidin-2-one 6. To a stirred solution of compound **5** (0.709 g, 1.89 mmol) in a 9:1 THF/MeOH mixture as solvent (22 mL) cooled at 0 °C, NaOH (4.2 mL of a 1 N aqueous solution, 4.2 mmol) was added dropwise. When the hydrolysis was completed (about 2 h, monitored by TLC), 1 N HCl was cautiously added until pH 7 was reached. The organic solvent was evaporated under vacuum, and the aqueous phase was extracted with 3×20 mL of DCM. The organic phase was dried over Na_2SO_4, the solvent was evaporated under vacuum, and the residue was purified by flash chromatography with a 60:40 hexanes/ethylacetate mixture as eluant. The product (0.592 g) was obtained in 94% yield as a white solid, mp 198–200 °C. IR: 3295, 1750 cm^{-1}. $[\alpha]_D^{23}$ −60.8 (*c* 0.72). ^{1}H NMR: δ 7.71 (B part of an AB system, *J* = 8.0 Hz, 2H), 6.88 (A part of an AB system, *J* = 8.0 Hz, 2H), 4.97 (d, *J* = 5.0 Hz, 1H), 4.43 (q, *J* = 7.0 Hz, 1H), 4.27 (dd, *J* = 7.0, 8.5 Hz, 1H), 4.24 (dd, *J* = 5.0, 7.0 Hz, 1H), 3.82 (dd, *J* = 7.0, 8.5 Hz, 1H), 3.79 (s, 3H), 1.70–1.33 (m, 10H). ^{13}C NMR: δ 166.0, 156.9, 130.4, 120.2, 114.2, 111.0, 76.6, 75.9, 65.7, 65.2, 55.4, 36.5, 34.8, 25.2, 24.1, 23.9. $C_{18}H_{23}NO_5$ requires: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.63; H, 6.78; N, 4.40.

(4*R*,4′*R*)-1-(4-Methoxyphenyl)-4-(1,4-dioxaspiro[4.5]dec-2-yl)azetidin-2,3-dione 7. P_2O_5 (0.070 g, 0.49 mmol) was added in one portion to anhydrous DMSO (2 mL) kept under nitrogen. After 5 min, a solution of compound **6** (0.117 g, 0.35 mmol) in anhydrous DMSO (1 mL) was added to the resulting mixture, and this was stirred at rt for 20 h. The reaction was monitored by TLC and small portions of P_2O_5 were added (if necessary) to drive the reaction to completion. The reaction mixture was then poured into a saturated aqueous solution of $NaHCO_3$ (30 mL), and the resulting solution was extracted with 3×10 mL of DCM. The combined organic extracts were dried over Na_2SO_4, the solvent was evaporated under vacuum, and the residue was purified by flash chromatography with a 60:40 hexanes/ethylacetate mixture as eluant. The product (0.098 g) was obtained in 85% yield as a yellow solid, mp 111–113 °C. IR: 1810, 1760 cm^{-1}. $[\alpha]_D^{23}$ −39.8 (*c* 0.62). ^{1}H NMR: δ 7.85 (B part of an AB system, *J* = 9.1 Hz, 2H), 6.98 (A part of an AB system, *J* = 9.1 Hz, 2H), 4.66 (d, *J* = 7.2 Hz, 1H), 4.33 (q, *J* = 7.2 Hz, 1H), 4.14 (AB system, *J* = 7.2, 8.0 Hz, 2H), 3.87 (s, 3H), 1.73–1.40 (m, 10H). ^{13}C NMR: δ 191.4, 60.0, 158.4, 130.6, 120.2, 114.6, 111.3, 75.1, 65.4, 55.7, 36.4, 34.8, 25.1, 24.2, 23.9. $C_{18}H_{21}NO_5$ requires: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.48; H, 6.55; N, 4.18.

(4*S*,4′*R*)-1-(4-Methoxyphenyl)-3-(4-phenylmethoxyphenylmethylidene)-4-(1,4-dioxaspiro[4.5] dec-2-yl)azetidin-2-one 8 (mixture of *E* and *Z* isomers). To a stirred suspension of 4-benzyloxybenzyl triphenylphosphonium bromide (0.240 g, 0.444 mmol) in anhydrous THF (5 mL), cooled at −20 °C and kept under nitrogen, BuLi (0.325 mL of a 1.5 M solution in hexanes) was added. The

mixture was stirred at −20 °C for 40 min, whereupon its color became bright red. Compound **7** (0.098 g, 0.296 mmol) in THF (5 mL) was then added dropwise at −20 °C, and the mixture was stirred for 2 h at that temperature. The reaction was then quenched by the addition of a saturated aqueous solution of NH_4Cl, and the aqueous layer was extracted with 2×20 mL of DCM. The combined organic extracts were dried over Na_2SO_4, the solvent was evaporated under vacuum, and the residue was purified by flash chromatography with a 80:20 hexanes/ethylacetate mixture as eluant. The product (0.111 g) was obtained in 73% yield as a 93:7 mixture of two isomers. $C_{32}H_{33}NO_5$ requires: C, 75.12; H, 6.50; N, 2.74. Found: C, 75.36; H, 6.78; N, 2.58. During the chromatographic separation pure fractions of each isomer were obtained. The major isomer had mp 113–115 °C. IR: 1740, 1511 cm^{-1}. $[\alpha]_D^{23}$ −181.0 (*c* 1.48). ^1H NMR: δ 7.54 (B part of an AB system, *J* = 9.2 Hz, 2H), 7.51 (B part of an AB system, *J* = 9.8 Hz, 2H), 7.43 (m, 5H),7.14 (d, *J* = 1.0 Hz, 1H), 6.99 (A part of an AB system, *J* = 9.2 Hz, 2H), 6.92 (A part of an AB system, *J* = 9.8 Hz, 2H), 5.29 (dd, *J* = 1.0, 4.3 Hz, 1H), 5.12 (s, 2H), 4.58 (dt, *J* = 6.4, 4.3 Hz, 1H), 3.83 (s, 3H), 3.77 (AB system, *J* = 8.0, 6.4 Hz, 2H), 1.60–1.30 (m, 10H). ^{13}C NMR: δ 160.5, 157.0, 136.5, 132.0, 131.9, 130.7, 128.6, 128.05, 127.4, 127.2, 118.7, 115.0, 114.2, 110.5, 76.6, 70.0, 65.4, 60.5, 55.5, 36.3, 34.8, 25.1, 24.0, 23.9. The minor isomer had mp 87–90 °C. IR: 1730, 1511 cm^{-1}. $[\alpha]_D^{23}$ 221.1 (*c* 0.34). ^1H NMR: δ 8.03 (B part of an AB system, *J* = 8.8 Hz, 2H), 7.67 (B part of an AB system, *J* = 9.2 Hz, 2H), 7.41 (m, 5H), 7.02 (A part of an AB system, *J* = 8.8 Hz, 2H), 6.92 (A part of an AB system, *J* = 9.2 Hz, 2H), 6.45 (s, 1H), 5.12 (s, 2H), 4.54 (d, *J* = 6.3 Hz, 1H), 4.52 (q, *J* = 6.4 Hz, 1H),), 4.11 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.97 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.83 (s, 3H), 1.70–1.35 (m, 10H). ^{13}C NMR: δ 162.0, 160.0, 156.2, 136.5, 132.6, 131.5, 131.1, 128.6, 127.4, 127.0, 126.2,118.9, 115.0, 114.4, 110.45, 75.3, 70.1, 65.4, 61.8, 55.5, 35.6, 34.6, 25.0, 23.8, 23.7.

(3*S*,4*S*,4′*R*)-1-(4-Methoxyphenyl)-3-(4-hydroxyphenylmethyl)-4-(1,4-dioxaspiro[4.5]dec-2-yl) azetidin-2-one 9. A suspension of compound **8** (0.090 g, 0.176 mmol) and 10% Pd/C (0.035 g) in absolute EtOH was shaken at RT under H_2 for 3 h. The mixture was then filtered through a Celite cake, that was thoroughly washed with DCM. The organic solvent was evaporated under vacuum The crude product (0.074 g) was obtained in quantitative yield as a white solid, mp 86–89 °C. IR: 3390, 1753 cm^{-1}. $[\alpha]_D^{23}$ −44.5 (*c* 0.4). ^1H NMR: δ 7.57 (B part of an AB system, *J* = 9.0 Hz, 2H), 7.14 (B part of an AB system, *J* = 8.4 Hz, 2H), 6.87 (A part of an AB system, *J* = 9.0 Hz, 2H), 6.77 (A part of an AB system, *J* = 8.4 Hz, 2H), 4.36 (q, *J* = 6.5 Hz, 1H), 4.22 (dd, *J* = 6.5, 5.0 Hz, 1H), 3.94 (dd, *J* = 8.5, 6.5 Hz, 1H), 3.81 (s, 3H), 3.74 (dt, *J* = 8.0, 5.0 Hz, 1H), 3.55 (dd, *J* = 8.5, 6.5 Hz, 1H), 3.19 (B part of an AB system, *J* = 8.0, 16.0 Hz, 1H), 2.88 (A part of an AB system, *J* = 8.0, 16.0 Hz, 1H), 1.67–1.30 (m, 10H). ^{13}C NMR: δ 167.55, 156.0, 154.7, 130.0, 129.5, 120.7, 119.8, 115.6, 113.7, 110.7, 75.8, 66.5, 58.6, 51.5, 55.5, 36.3, 34.6, 30.3, 25.0, 23.9, 23.8. $C_{25}H_{29}NO_5$ requires: C, 70.90; H, 6.90; N, 3.31. Found: C, 71.08; H, 6.88; N, 3.49. This reaction was best carried out with a fresh, active sample of catalyst. The use of less active catalysts required longer reaction times and in some cases led to the formation of minor amounts (about 10%) of a *trans* β-lactam. This had ^1H NMR: δ 7.58 (B part of an AB system, *J* = 9.0 Hz, 2H), 7.11 (B part of an AB system, *J* = 8.4 Hz, 2H), 6.87 (A part of an AB system, *J* = 9.0 Hz, 2H), 6.77 (A part of an AB system, *J* = 8.4 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 1H), 3.83 (dd, *J* = 7.5, 2.1 Hz, 1H), 3.81 (s, 3H), 3.74 (dd, *J* = 8.6, 7.1 Hz, 1H), 3.15 (B part of an AB system, *J* = 13.5, 8.9 Hz, 1H), 3.08 (dt, *J* = 8.9, 2.1 Hz, 1H), 3.04 (dd, *J* = 8.6, 7.1 Hz, 1H), 2.83 (A part of an AB system, *J* = 13.5, 8.9 Hz, 1H), 1.67–130 (m, 10H).

(3S,4*S*,4′*R*)-1-(4-Methoxyphenyl)-3-[4-(2-propenyloxy)-phenylmethyl]-4-(1,4-dioxaspiro[4.5]dec-2-yl) azetidin-2-one 10. A mixture of compound **9** (0.060 g, 0.142 mmol), allylbromide (0.041 mL, 0.469 mmol), K_2CO_3 (0.065 g, 0.469 mmol) in acetonitrile (4 mL) was stirred at 50 °C for 60 h. The solvent was then evaporated under vacuum and the residue was taken up in DCM (10 mL). The solid was filtered off and the filtrate was concentrated under vacuum. The crude product was purified by flash chromatography with a 70:30 hexanes/ethylacetate mixture as eluant. The product (0.066 g) was obtained in quantitative yield as a waxy, pale yellow solid. IR: 1746, 1513 cm^{-1}. $[\alpha]_D^{23}$ −66.7 (*c* 1.32). ^1H NMR: δ 7.56 (B part of an AB system, *J* = 9.0 Hz, 2H), 7.20 (B part of an AB system, *J* = 8.4 Hz, 2H), 6.85 (A part of an AB system, *J* = 9.0 Hz, 4H), 6.08 (m, 1H), 5.43 (ddt, *J* = 16.0, 3.0, 1.6 Hz, 1H), 5.29 (dd, *J* = 12.0, 3.0 Hz, 1H), 4.58–4.51 (m, 2H), 4.33 (q, *J* = 7.5 Hz, 1H), 4.21 (dd, *J* = 7.5, 6.0 Hz, 1H), 3.89 (dd, *J* = 8.5, 7.5 Hz, 1H), 3.73 (dt, *J* = 8.0, 6.0 Hz, 1H), 3.66 (s, 3H), 3.50 (dd, *J* = 8.5, 7.5 Hz, 1H), 3.23 (B part of an AB system, *J* = 8.0, 16.0 Hz, 1H), 2.90 (A part of an AB system, *J* = 8.0, 16.0 Hz, 1H), 1.67–1.30 (m, 10H). ^{13}C NMR: δ 167.4, 157.6, 156.5, 133.0, 131.5, 130.4, 129.4, 120.7, 117.8, 115.1, 113.9, 110.7, 75.9, 69.0, 66.7, 58.6, 55.6, 51.7, 36.4, 34.6, 30.3, 25.2, 24.1, 23.9. $C_{28}H_{33}NO_5$ requires: C, 72.55; H, 7.17; N, 3.02. Found: C, 72.27; H, 7.33; N, 2.87.

(3*S*,4*S*)-1-(4-Methoxyphenyl)-3-[4-(2-propenyloxy)phenylmethyl]-4-formylazetidin-2-one 12. Ketal hydrolysis. A solution of compound **10** (0.060 g, 0.129 mmol) in a 1:1 TFA/water mixture (4 mL) was stirred overnight while allowing the reaction temperature to rise from 0 °C to rt. Solid K_2CO_3 was then added until gas evolution had subsided. The mixture was then extracted with 3×5 mL of EtOAc. The combined organic extracts were washed with a saturated aqueous solution of Na_2CO_3 and dried over Na_2SO_4. The solvent was evaporated under vacuum to give the crude product that was used without further purification.

Diol oxidation. To a stirred solution of diol in a 1:1 EtOAc/water mixture (4 mL) cooled at 0 °C, solid $NaIO_4$ (0.110 g, 0.516 mmol) was added in one portion. The mixture was monitored by TLC. After about 2 h stirring at 0 °C, the mixture was extracted with 3×5 mL of EtOAc. The combined organic extracts were dried over Na_2SO_4, the solvent was evaporated under

vacuum, and the crude product was purified by flash chromatography with a 70:30 hexanes/EtOAc mixture as eluant. Aldehyde **12** (0.033 g), a thick oil, was thus obtained in 73% yield from compound **10**. IR: 1746, 1690 cm^{-1}. $[\alpha]_D^{23}$ −39.3 (*c* 0.28). ^1H NMR: δ 9.64 (d, *J* = 2.8 Hz, 1H), 7.24 (B part of an AB system, *J* = 9.0 Hz, 2H), 7.17 (B part of an AB system, *J* = 8.6 Hz, 2H), 6.89 (A part of an AB system, *J* = 9.0 Hz, 2H), 6.88 (A part of an AB system, *J* = 8.6 Hz, 2H), 6.10–6.00 (m, 1H), 5.43 (dq, *J* = 17.0, 1.6 Hz, 1H), 5.29 (dq, *J* = 10.3, 1.4 Hz, 1H), 4.57 (dd, *J* = 6.1, 2.8 Hz, 1H), 4.59–4.51 (m, 2H), 4.03 (dt, *J* = 9.3, 6.7 Hz, 1H), 3.88 (s, 3H), 3.20 (B part of an AB system, *J* = 15.0, 6.7 Hz, 1H), 2.93 (A part of an AB system, *J* = 15.0, 6.7 Hz, 1H). ^{13}C NMR: δ 199.1, 165.0, 157.5,157.4, 133.2, 131.5, 130.0, 129.7, 117.8, 117.7, 115.1, 114.4, 68.8, 60.0, 55.5, 55.0, 30.3. $C_{21}H_{21}NO_4$ requires: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.70; H, 6.22; N, 3.83.

(3*S*,4*S*)-1-(4-Methoxyphenyl)-3-[4-(2-propenyloxy)phenylmethyl]-4-benzyloxycarbonyl azetidin-2-one 14. Aldehyde oxidation. A mixture of aldehyde **12** (0.0351 g, 0.1 mmol), CrO_3 (0.100 g, 1 mmol), concentrated sulfuric acid (0.026 mL), water (56 mL), and acetone (5 mL) was stirred at rt for 15 min. The mixture was then extracted with EtOAc (2×15 mL), and the combined organic phases were washed with water and dried over Na_2SO_4. The solvent was evaporated under vacuum to give the crude acid **13** that was used without further purification.

Ester formation. To a solution of **13** in acetone (10 mL), benzylbromide (0.0142 mL, 0.12 mmol) and K_2CO_3 (0.030 g, 0.22 mmol) were added in this order. The mixture was stirred at rt for 2.5 h. The solvent was then evaporated under vacuum, and EtOAc (20 mL) was added to the residue. Water was then added, and the organic phase was separated and washed with a saturated aqueous solution of NaCl. The separated organic phase was dried over Na_2SO_4. The solvent was evaporated under vacuum to give the crude ester that was purified by flash chromatography with a 90:10 and then 70:30 hexanes/EtOAc mixture as eluant. Ester **14** (0.031 g), a thick oil, was thus obtained in 68% yield from compound **12**. IR: 1752 cm^{-1}. $[\alpha]_D^{23}$ −20.4 (*c* 0.1). ^1H NMR: δ 7.30–7.39 (m, 5H), 7.19–7.27 (m, 6H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.05–6.10 (m, 1H), 5.42 (dq, *J* = 17.0, 1.6 Hz, 1H), 5.28 (dq, *J* = 10.3, 1.4 Hz, 1H), 5.16 (B part of an AB system, *J* = 10.3 Hz, 1H), 5.02 (A part of an AB system, *J* = 10.3 Hz, 1H), 4.63 (d, *J* = 5.0 Hz, 1H), 4.51 (bd, *J* = 5.4 Hz, 2H), 4.03 (ddd, *J* = 9.0, 6.7, 5.0 Hz, 1H), 3.80 (s, 3H), 3.12 (B part of an AB system, *J* = 15.0, 6.7 Hz, 1H), 2.90 (A part of an AB system, *J* = 15.0, 9.0 Hz, 1H). ^{13}C NMR: δ 169.3, 165.1, 154.4, 154.3, 133.0, 129.5, 129.4, 128.6, 128.2, 127.1, 126.4, 118.5, 117.9, 114.8, 114.4, 113.1, 67.5, 60.1, 55.5, 55.0, 50.8, 30.9. $C_{28}H_{27}NO_5$ requires: C, 73.50; H, 5.95; N, 3.06. Found: C, 73.78; H, 6.13; N, 2.94.

(3*S*,4*S*)-1-(4-Methoxyphenyl)-3-[4-[(1,1-dimethyethyl)diphenylsilyl]oxy]phenylmethyl]-4-benzyloxycarbonyl azetidin-2-one 16. Allyl group removal. A mixture of compound **14** (0.018 g, 0.0394 mmol), $Pd(OAc)_2$ (0.001 g, 0.0044 mmol), and triphenylphosphine (0.005 g, 0.019 mmol) in EtOH (1 mL) was refluxed for 60 min. To the cooled mixture wet SiO_2 (ca. 0.2 g) was added and the resulting slurry was stirred at rt for 5 min. The mixture was then diluted with EtOH (10 mL), filtered through a Celite cake, and concentrated under vacuum. The residue was filtered through a short column of silica gel with a 75:25 hexanes/EtOAc mixture as eluant to give the crude phenol **15** (^1H NMR: δ 7.38–7.29 (m, 5H), 7.25–7.18 (m, 6H), 6.85 (d, *J* = 9.0 Hz, 2H), 5.20 (B part of an AB system, *J* = 12.0 Hz, 1H), 4.98 (A part of an AB system, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 6.0 Hz, 1H), 3.97 (ddd, *J* = 10.0, 6.8, 6.0 Hz, 1H), 3.80 (s, 3H), 3.23 (B part of an AB system, *J* = 15.0, 6.8 Hz, 1H), 2.95 (A part of an AB system, *J* = 15.0, 10.0 Hz, 1H) that was used as such in the following step.

Silylation. To a stirred solution of crude phenol **15** in DCM (1 mL), *t*-butyldiphenylchlorosilane (0.010 mL, 0.0394 mmol) and imidazole (0.005 g, 0.073 mmol) were added in this order. After 3 h stirring at rt, the same amounts of silylating agent and imidazole, dissolved in DCM (1 mL), were added, and stirring was continued overnight. Water (1 mL) and DCM (5 mL) were then added, the organic phase was separated, washed with water (2 mL), and dried over over Na_2SO_4. The solvent was evaporated under vacuum to give the crude product that was purified by flash chromatography with 90:10, then 70:30, then 30:70 mixtures of hexanes and EtOAc as eluants. The product **16** (0.013 g, 51%) was obtained as an oil. IR: 1750 cm^{-1}. $[\alpha]_D^{23}$ 16.3 (*c* 0.05). ^1H NMR: δ 7.65–7.76 (m, 5H), 7.43–7.28 (m, 10H), 7.19 (B part of an AB system, *J* = 8.8 Hz, 2H), 6.93 (B part of an AB system, *J* = 8.8 Hz, 2H), 6.83 (A part of an AB system, *J* = 8.8 Hz, 2H), 6.70 (A part of an AB system, *J* = 8.8 Hz, 2H), 5.15 (B part of an AB system, *J* = 12.1 Hz, 1H), 4.88 (A part of an AB system, *J* = 12.1 Hz, 1H), 4.58 (d, *J* = 6.0 Hz, 1H), 3.87 (dt, *J* = 9.3, 6.0 Hz, 1H), 3.79 (s, 3H), 3.08 (B part of an AB system, *J* = 15.0, 6.0 Hz, 1H), 2.81 (A part of an AB system, *J* = 15.0, 9.3 Hz, 1H), 1.11 (s, 9H). ^{13}C NMR: δ 169.0, 165.0, 156.7, 154.0, 136.5, 134.5, 132.0, 130.0, 129.8, 129.3, 129.0, 128.5, 120.0, 118.0, 115.5, 67.5, 55.5, 55.0, 53.0, 30.0, 26.5, 18.0. $C_{41}H_{41}NO_5Si$ requires: C, 75.08; H, 6.30; N, 2.14. Found: C, 75.36; H, 6.43; N, 2.02.

(3*S*,4*S*)-3-[4-[(1,1-Dimethyethyl)diphenylsilyl]oxy]phenylmethyl]-4-benzyloxycarbonyl azetidin-2-one 2. To a stirred solution of compound **16** (0.012 g, 0.0183 mmol) in acetonitrile (2 mL) cooled at −20 °C, CAN (0.040 g, 0.073 mmol) in water (1.0 mL) was added in one portion. After 0.5 h stirring at a reaction temperature ranging from −20 to −10 °C, the reaction was quenched by the addition of saturated aqueous solutions of $NaHSO_3$ and $NaHCO_3$. The mixture was extracted with diethylether (2×10 mL), and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated under vacuum to give the crude product that was purified by flash chromatography with a 70:30 mixture of hexanes and EtOAc as eluants. The product 2 (0.007 g, 70%) was obtained as very thick oil that solidified while stored in the freezer. IR: 3295, 1755 cm^{-1}. $[\alpha]_D^{23}$ 12.0

(*c* 0.05). ^{1}H NMR: δ 7.55–7.45 (m, 4H), 7.40–7.25 (m, 11H), 6.91 (B part of an AB system, $J=8.5$ Hz, 2H), 6.69 (A part of an AB system, $J=8.5$ Hz, 2H), 5.95 (bs, 1H), 5.13 (B part of an AB system, $J=12.1$ Hz, 1H), 4.87 (A part of an AB system, $J=12.1$ Hz, 1H), 4.30 (d, $J=6.0$ Hz, 1H), 3.85 (q, $J=6.0$ Hz, 1H), 2.97 (B part of an AB system, $J=15.0$, 6.0 Hz, 1H), 2.73 (A part of an AB system, $J=15.0$, 6.0 Hz, 1H), 1.11 (s, 9H). ^{13}C NMR: δ 170.5, 169.5, 155.0, 136.0, 135.0, 134.0, 132.0, 130.0, 129.0, 128.5, 119.5, 67.5, 56.0, 52.5, 31.0, 26.5, 19.0. $C_{34}H_{35}NO_4Si$ requires: C, 74.28; H, 6.42; N, 2.55. Found: C, 74.44; H, 6.51; N, 2.38.

Acknowledgement

We thank MURST (Progetto Nazionale Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni) and CNR for financial support.

References and Notes

1. (a) Firestone, R. A.; Barker, P. L.; Pisano, J. M.; Ashe, B. M.; Dahlgren, M. E. *Tetrahedron* **1990**, *46*, 2255. (b) Shah, S. K.; Dorn, C. P., Jr.; Finke, P. E.; Hale, J. J.; Hagmann, W. K.; Brause, K. A.; Chandler, G. O.; Kissinger, B. M.; Weston, H.; Knight, W. B.; Maycock, A. L.; Dellea, P. S.; Fletcher, D. S.; Hand, K. M.; Mumford, R. A.; Underwood, D. J.; Doherty, J. B. *J. Med. Chem.* **1992**, *35*, 3745. (c) Han, W. T.; Trehan, A. K.; Wright, J. K. K.; Federici, M. E.; Seiler, S. M.; Meanwell, N. A. *Bioorg. Med. Chem.* **1995**, *3*, 1123. (d) Wu, Z.; Georg, G. I.; Cathers, B. E.; Schloss, J. V. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 983. (e) Pitlik, J.; Townsend, C. A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3129. (f) Borthwick, A. D.; Weingarten, G.; Haley, T. M.; Tomaszewski, M.; Wang, W.; Hu, Z.; Bedard, J.; Jin, H.; Yuen, L.; Mansour, T. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 365. (g) Deziel, R.; Malenfant, E. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1437. (h) Yoakim, C.; Ogilvie, W. W.; Cameron, D. R.; Chabot, C.; Guse, I.; Hachè, B.; Naud, J.; O'Meara, J. A.; Plante, R.; Deziel, R. *J. Med. Chem.* **1998**, *41*, 2882. (i) Wilmouth, R. C.; Westwood, N. J.; Anderson, K.; Brownlee, W.; Claridge, T. D. W.; Clifton, I. J.; Pritchard, G. J.; Aplin, R. T.; Schofield, C. J. *Biochemistry* **1998**, *37*, 17506. (j) Bonneau, P. R.; Hasani, F.; Plouffe, C.; Malenfant, E.; LaPlante, S. R.; Guse, I.; Ogilvie, W. W.; Plante, R.; Davidson, W. C.; Hopkins, J. L.; Morelock, M. M.; Cordingley, M. G.; Deziel, R. *J. Am. Chem. Soc.* **1999**, *121*, 2965. (k) La Plante, S. R.; Bonneau, P. R.; Aubry, N.; Cameron, D. R.; Deziel, R.; Grand-Maitre, C.; Plouffe, C.; Tong, L.; Kawai, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 2974. (l) Ogilvie, W. W.; Yoakim, C.; Do, F.; Hache, B.; Lagace, L.; Naud, J.; O'Meara, J. A.; Deziel, R. *Bioorg. Med. Chem.* **1999**, *7*, 1521. (m) Taylor, P.; Anderson, V.; Dowden, J.; Flitsch, S. L.; Turner, N. J.; Loughran, K.; Walkinnshaw, M. D. *J. Biol. Chem.* **1999**, *274*, 24901. (n) Imming, P.; Klar, P.; Dix, D. *J. Med. Chem.* **2000**, *43*, 4328. (o) Achilles, K.; Schneider, M.; Schirmeister, T.; Otto, H. H. *Pharmazie* **2000**, *55*, 798. (p) Demarcus, M.; Ganadu, M. L.; Mura, G. M.; Porcheddu, A.; Quaranta, L.; Reginato, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 697. (q) Beardsell, M.; Hinchliffe, P. S.; Wood, J. M.; Wilmouth, R. C.; Schofield, C. J.; Page, M. I. *J. Chem. Soc. Chem. Commun.* **2001**.

2. Adlington, R. M.; Baldwin, J. E.; Chen, B.; Cooper, S. L.; McCoull, W.; Pritchard, G. J.; Howe, T. J.; Becker, G. W.; Hermann, R. B.; McNulty, A. M.; Neubauer, B. L. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1689.

3. Oestering, J. E. *J. Urol* **1991**, *145*, 907, and references therein.

4. (a) Peehl, D. M. *Cancer* **1995**, *75*, 2021. (b) Diamandis, E. P.; Yu, H. *J. Clin. Endocrinol. Metab.* **1995**, *80*, 1515.

5. (a) Review: Benaglia, M.; Cinquini, M.; Cozzi, F. *Eur. J. Org. Chem* **2000**, 563. (b) For a reference particularly relevant to this work, see: Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G. *J. Org. Chem.* **1992**, *57*, 4155. (c) For recent applications not included in ref 5a, see: Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Poletti, L.; Raimondi, L.; Perboni, A. *Eur. J. Org. Chem* **1999**, 3067. (d) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. *Tetrahedron: Asymmetry* **1999**, *10*, 4841.

6. Indeed, condensation of the titanium enolate of the 2-pyridylthioester derived from 4-allyloxy hydrocinnamic acid with the *N*-4-methoxyphenylimine derived from ethylglyoxylate gave a 50:50 mixture of *trans* and *cis* β-lactams in 70% yield.

7. (a) The synthesis of (*S*)-*O*,*O*-cyclohexylideneglyceraldehyde has been described: Grauert, M.; Schöllkopf, U. *Liebigs Ann. Chem.* **1985**, 1817. (b) Yoshida, J.; Nagakawa, M.; Seki, H.; Hino, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 343. (c) However, in our hands, only the application of the method described in ref 7a afforded the product in good and reproducible yields. Modification of a procedure employed to obtained (*S*)-glyceraldehyde acetonide [Jung, M. E.; Shaw, T. J. *J. Am. Chem. Soc.* **1980**, *102*, 6304] was also ineffective.

8. Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Carreaux, F.; Cuevas, C.; Maneiro, E.; Ontoria, J. M. *J. Org. Chem.* **1994**, *59*, 3123.

9. The direct conversion of diol **11** into acid **13**, attempted following the procedure described by Palomo et al. for related compounds (Palomo, C.; Aizpurua, J. M.; Mielgo, A.; Linden, A. *J. Org. Chem.* **1996**, *61*, 9186) led to extensive product decomposition..

10. Georg, G. I.; Kant, J.; Gill, H. S. *J. Am. Chem. Soc.* **1987**, *109*, 1129.

11. Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Ponzini, F.; Raimondi, L. *Tetrahedron* **1994**, *50*, 2939.

12. The assignment of configuration to this and other titanium enolates was based on NMR experiment as described in ref 5b. Very recently, this assignment has independently been confirmed: Cooke, J. W. B.; Berry, M. B.; Caine, D. M.; Cardwell, K. S.; Cook, J. S.; Hodgson, A. *J. Org. Chem.* **2001**, *66*, 334.

13. (a) For recent reviews, see: Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377. (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem* **1999**, 3223.

14. Barton, D. H. R.; Chow, Y. L.; Cox, A.; Kirby, G. W. *J. Chem. Soc.* **1965**, 3571.