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Diastereoselective synthesis of 2-substituted-piperidin-4-ones as convenient precursors for an asymmetric approach to carbacephams

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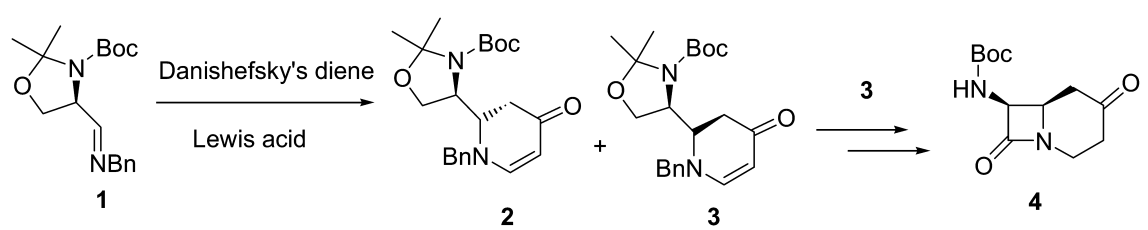
Abstract—Optically active carbacephams can be efficiently prepared generating the β-lactam ring on 2-substituted-piperidin-4-ones. These can, in turn, be prepared diastereoselectively through a Michael–Michael reaction sequence initiated by benzylamine on precursors derived by Wittig reaction between serinals and 4-[(4-methylphenyl)sulfonyl]-1-(triphenylphosphoranylidene)-2-butanone.

1. Introduction

The extensive use of common β-lactam antibiotics has resulted in an increasing number of resistant strains of bacteria through mutation and β-lactamase gene transfer, thus triggering a continuous interest in the synthesis of new β-lactam systems.[1] Over the past few years, the literature has indicated a growing interest in the preparation and biological evaluation of carbacephalosphorins (carbacephems), and one of them, loracarbef, has been developed and marketed.[2] Most of the synthetic approaches to the basic skeleton of carbacepham nucleus relied on the construction of the six-membered ring system into the existing β-lactam ring, usually obtained through classical Staudinger reaction.[3] Recently, synthetic pathways involving the construction of the six-membered ring system followed by formation of the β-lactam ring have been successfully exploited as alternative approaches to the asymmetric synthesis of carbacephams.[4,5] An example of the latter strategy has been recently reported by Avenoza et al.[6] who accomplished a short and efficient asymmetric approach to the carbacepham derivative **4**, involving as the key step the asymmetric hetero Diels–Alder reaction between the benzylimine **1**, derived from the Garner's aldehyde, and Danishefsky's diene (Scheme 1). The diastereomeric mixture of the appropriately substituted six-membered ring systems **2** and **3** was separated by column chromatography and the major cyclo-adduct **3** was eventually utilized for the subsequent construction of the β-lactam ring of **4**, which represents a useful building block for further modifications.

2. Results and discussion

We have recently introduced[7] 4-[(4-methylphenyl)sulfonyl]-1-(triphenylphosphoranylidene)-2-butanone **5** as a readily available four-carbon synthon for substituted divinyl



Scheme 1.

Keywords: carbacephams; diastereoselection; 2-substituted-piperidin-4-ones.
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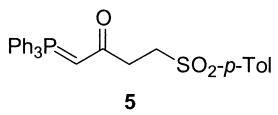


Figure 1.

ketones, the two double bonds adjacent to the central carbonyl group being generated by Wittig reaction of the stabilized ylide function with a suitable aldehyde and through a base-promoted β-elimination of the sulfone moiety, respectively (Fig. 1).

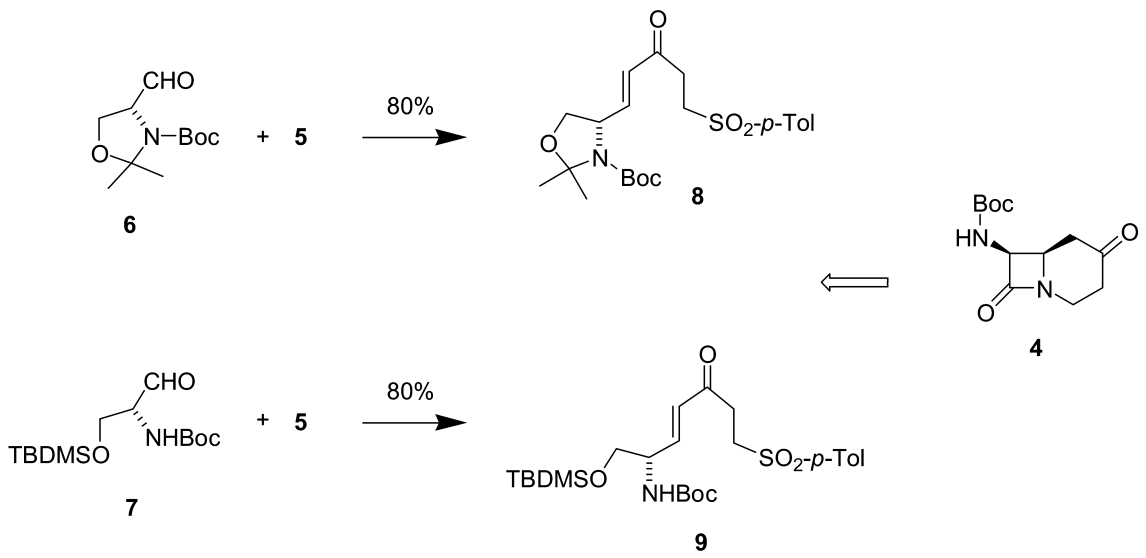
The derived divinyl ketones are able to take part to domino reaction sequences leading to an efficient construction of 2-substituted 4-piperidone ring systems when nitrogen nucleophiles (e.g. benzylamine) were used as the initiators.[8]

We wish to report in this paper a convenient alternative approach to the asymmetric synthesis of **4** which we envisaged as an extension of our own interest in the synthesis of piperidine derivatives via tandem Michael–Michael reactions.[7]

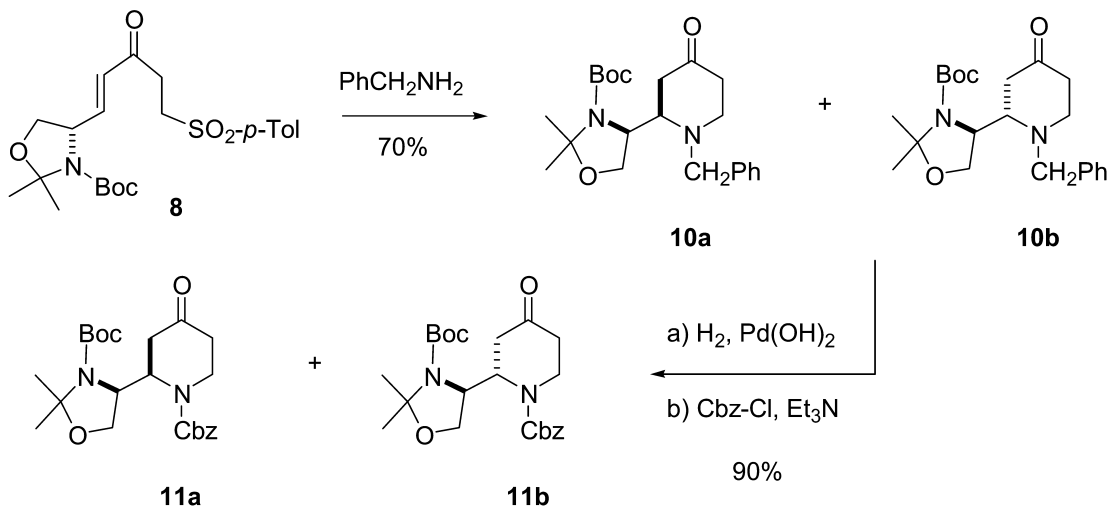
Our own approach to the preparation of **4** calls for both compound **8** and **9** as the requisite starting materials. These were readily obtained in 80% yield by reaction between the synthon **5**[7] and both the Garner aldehyde **6**[9] and the *N*-Boc-*O*-*tert*-butyldimethylsilyl (*O*-TBDMS) protected serinal **7**[10] (Scheme 2).

The reaction of **8** with benzylamine (Scheme 3) proceeded uneventfully through two sequential Michael reactions producing a diastereomeric mixture of the piperidones **10a** and **10b**, the relative stereochemistry for both compounds being assigned on the basis of the results obtained only in a later stage of the synthesis. In particular, a 6:4 epimeric mixture of piperidones **10a** and **10b** was obtained at room temperature for 48 h, while a 9:1 ratio was observed when the reaction was carried out at 0°C for 6 days, the diastereomeric ratio being determined in all cases through HPLC analysis.

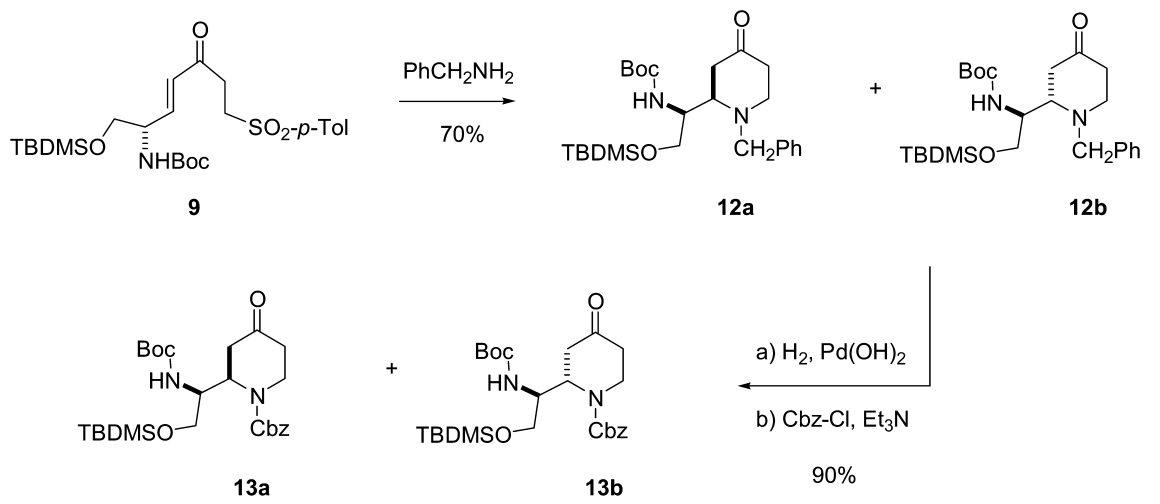
In order to increase the diastereoselectivity of the process, we examined the reaction of **8** with chiral amines, such as (+) and (−)-phenylethylamine, instead of benzylamine,



Scheme 2.



Scheme 3.



Scheme 4.

under the same conditions as above. Disappointingly, the expected epimeric piperidinones were formed in the same 6:4 ratio as when the reaction was performed at room temperature, while no reaction was observed at 0°C.

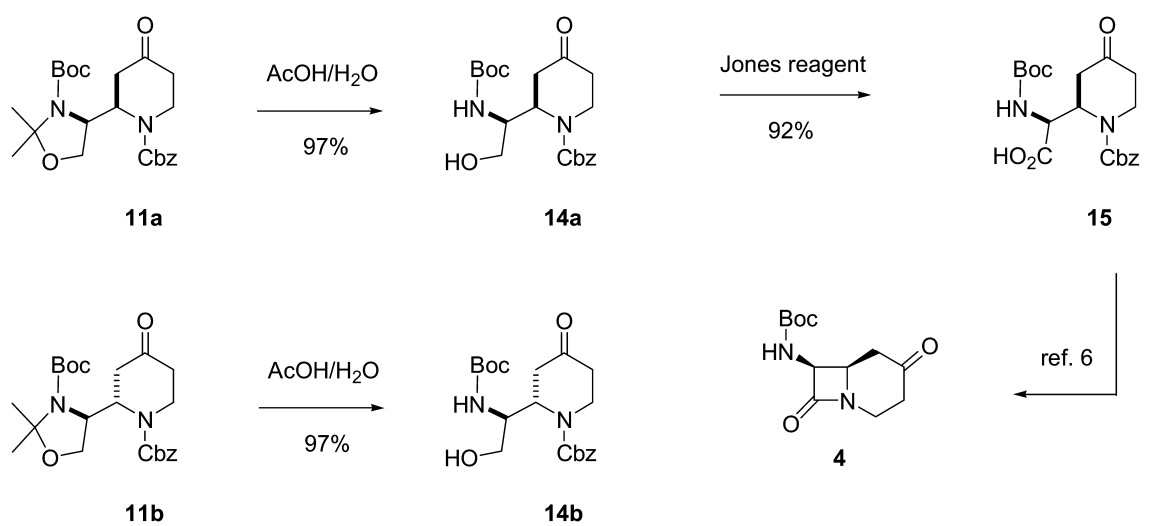
The mixture of *N*-benzyl derivatives **10a** and **10b** was subsequently transformed in quantitative yield into the corresponding mixture of *N*-Cbz derivatives **11a** and **11b**, which could be separated by flash chromatography. Interestingly, a reversal of the diastereoselectivity was observed when the tandem Michael reaction sequence was performed on the precursor **9**, deriving from the reaction of the differently protected serinal **7** (*N*-Boc-*O*-TBDMS) with phosphorane **5**. Indeed, when **9** was exposed to reaction with benzylamine at 0°C, an inseparable 2:10 mixture of the piperidones **12a** and **12b** (HPLC ratio) was obtained. Clean separation was then accomplished by flash chromatography after transformation into the corresponding *N*-Cbz derivatives **13a** and **13b** (Scheme 4).

Cleavage of the *N*,*O*-acetal of the intermediates **11a** and **11b**, easily achieved by treatment with acetic acid/water, gave the 1,2-amino alcohols **14a** and **14b**, respectively, the mild acid hydrolysis preserving the *N*-Boc protecting group (Scheme 5). The primary alcohol group of the prevalent isomer was then oxidized by means of Jones reagent producing the known acid **15**, already transformed by Avenoza[6] into the interesting carbacepham derivative **4**.

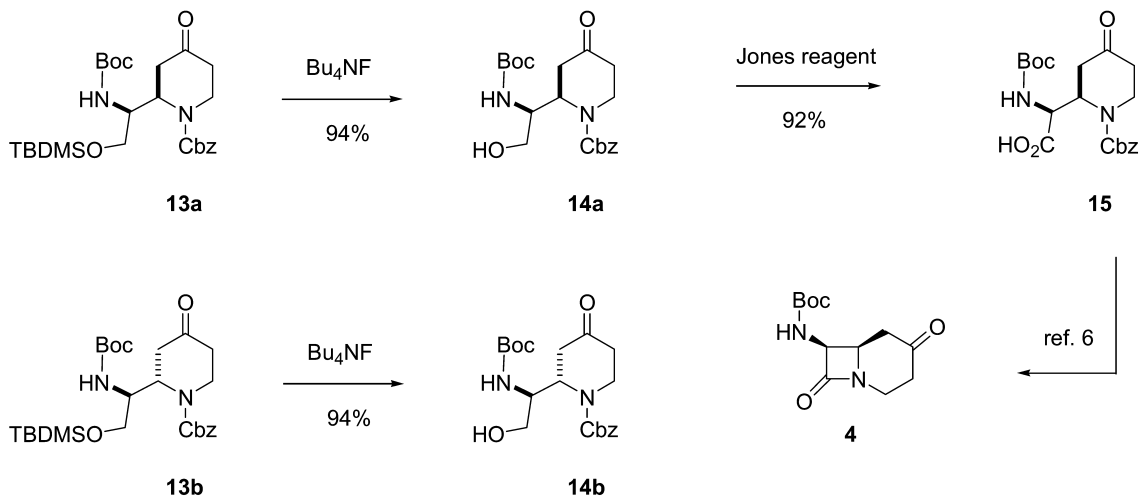
Moreover, submitting compound **13b** and **13a** to the action of tetrabutylammonium fluoride, the *O*-silyl protective group was smoothly removed to furnish the primary alcohols **14b** and **14a**, the latter being easily converted to the acid **15** (Scheme 6), possessing spectroscopic and optical features identical to those reported by Avenoza et al.[6]

3. Conclusions

In summary, we have shown that it is possible to obtain optically active functionalized carbacephams using the Wittig reaction between serinals and 4-[(4-methylphenyl)-sulfonyl]-1-(triphenylphosphoranylidene)-2-butanone **5** as a tool to prepare the required precursors able to participate to a domino reaction sequence initiated by benzylamine for the generation of the suitable substituted six-membered ring on which the β-lactam ring could be subsequently constructed. These results emphasize once more the versatility of the



Scheme 5.



Scheme 6.

building block **5** as a valuable tool for the construction of functionalized carbon frameworks particularly useful as precursors of substituted piperidine ring systems, one of the commonest structural sub-units in biologically active natural compounds. We believe that the asymmetric synthesis of carbacephams described in this paper, which compares well with the Avenoza's in terms of steps and overall yield, could be considered of high potential value for the stereocontrolled route to piperidine systems.

4. Experimental

4.1. General remarks

Melting points were determined on a Büchi–Tottoli apparatus and are uncorrected. Infrared (IR) spectra were recorded on a FT-IR Bruker IFS 88 spectrometer. Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were taken on a Bruker AC spectrometer (200 and 50 MHz) and on a Varian 300 Unity spectrometer (300 and 75 MHz) for solutions in $CDCl_3$ unless otherwise noted. Chemical shifts are given in parts per million downfield from tetramethylsilane as the internal standard and coupling constants are given in Hertz. Optical rotations were measured with a Perkin–Elmer 241 MC polarimeter. Diastereomeric ratios were determined through HPLC analyses, in normal phase on silica gel and isopropanol/water 80:20 as eluant, in reverse phase on C18 and acetonitrile/water concentration gradient, using a DG 1680-54 JASCO UV 1575 instrument. Organic solutions were dried over anhydrous magnesium sulfate and evaporated with a rotary evaporator. Light petroleum refers to the fractions boiling in the range 40–60°C and ether to diethyl ether. Flash-chromatography was carried out with Merck silica gel (230–400 mesh). All reactions were performed under N_2 or Ar atmosphere. Elemental analyses were effected by the micro analytical laboratory of Dipartimento di Chimica, University of Ferrara.

4.1.1. (4*S*)-4-[3-Oxo-5-(4′-methylphenylsulfonyl)-1-pentenyl]-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-oxazolidine (8). A mixture of phosphorane **5**[7] (1.55 g, 3.18 mmol) and the aldehyde **6** (0.73 g, 3.18 mmol) in dry $CHCl_3$ (10 mL) was refluxed for 20 h, then concentrated in vacuo. The oily residue was purified by flash-chromatography (eluent: EtOAc/cyclohexane 1:1), affording the title compound **8** (1.11 g, 80%) as an oil. LRMS (EI): found 437.4; $C_{22}H_{31}NO_6S$ requires 437.2. [Found: C, 60.29; H, 7.05. $C_{22}H_{31}NO_6S$ requires C, 60.39; H, 7.14%]. $[\alpha]_D^{20}$=+58.5 (*c* 0.65, $CHCl_3$). ν_{max} (liquid film) 1690, 1680, 1625, 1590 cm^{-1}; δ_H (300 MHz, DMSO-d$_6$, 120°C) 1.42 (9H, s, 3*Me*), 1.48 (3H, s, *Me*), 1.55 (3H, s, *Me*), 2.42 (3H, s, Ph*Me*), 2.97 (2H, t, *J*=7.08 Hz, CH_2SO$_2$), 3.49 (2H, t, *J*=7.08 Hz, CH_2CO), 3.80 (1H, dd, *J*=9.1, 2.7 Hz, CH_aH$_b$O), 4.10 (1H, dd, *J*=9.1, 6.6 Hz, CH$_a$$H_b$O), 4.47 (1H, m, C*H*NBoc), 6.15 (1H, dd, *J*=15.9, 1.2 Hz, HC=C*H*–CO), 6.70 (1H, dd, *J*=15.9, 6.3 Hz, *H*C=CH–CO), 7.45 (2H, d, *J*=8.1 Hz, arom.), 7.80 (2H, d, *J*=8.1 Hz, arom.); δ_C (50 MHz, $CDCl_3$, 25°C) 21.5, 24.5, 26.4, 28.3, 32.9, 50.6, 58.1, 67.2, 77.1, 80.8, 94.5, 127.9, 129.2, 135.9, 144.9, 145.5, 151.9, 194.9.

4.1.2. (4*S*,2′*R*)-4-(1′-Benzyl-4′-oxo-piperidin-2′-yl)-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-oxazolidine (10a) and (4*S*,2′*S*)-4-(1′-benzyl-4′-oxo-piperidin-2′-yl)-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-oxazolidine (10b). Benzylamine (0.81 g, 7.60 mmol) was added to a solution of **8** (1.66 g, 3.80 mmol) in THF (10 mL), the mixture stirred at 0°C for 6 days, then concentrated in vacuo. The oily residue was dissolved in EtOAc (20 mL), washed with $NaHCO_3$ solution (2×10 mL, sat. aq.) and brine (2×10 mL). The dried organic extracts were concentrated and the residue purified by flash chromatography (eluent: EtOAc/cyclohexane 1:4) affording the oily mixture of the title compounds **10a** and **10b** (1.03 g, 70%) in 9:1 ratio (HPLC analysis). A pure fraction of **10a** could be obtained and characterized. LRMS (EI): found 388.1; $C_{22}H_{32}N_2O_4$ requires 388.2. [Found: C, 67.94; H, 8.27. $C_{22}H_{32}N_2O_4$ requires C, 68.01; H, 8.30%]. $[\alpha]_D^{20}$=+28.5 (*c* 0.40, $CHCl_3$). ν_{max} (liquid film) 1710, 1680 cm^{-1}; δ_H (300 MHz, DMSO-d$_6$,160°C) 1.40 (9H, s, 3*Me*), 1.45 (3H, s, *Me*), 1.58 (3H, s, *Me*), 2.30–2.38 (2H, m, CH_2CO), 2.40–2.49 (2H, m, COCH_2), 3.10–3.23 (2H, m, CH_2N), 3.31–3.40 (1H, m, C*H*N), 3.60 (1H, d, *J*=14.0 Hz, CH_aH$_b$Ph), 3.96 (1H, dd, *J*=9.5, 3.0 Hz, CH$_a$$H_b$O), 4.05 (1H, d, *J*=14.0 Hz, CH$_a$$H_b$Ph), 4.10 (1H, dd, *J*=9.5, 2.0 Hz, CH$_a$$H_b$O), 4.27 (1H, m, C*H*NBoc), 7.15–7.45 (5H, m, arom.).

4.1.3. (4*S*,2′*R*)-4-(1′-Benzyloxycarbonyl-4′-oxo-piperidin-2′-yl)-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-oxazolidine (11a) and (4*S*,2′*S*)-4-(1′-benzyloxycarbonyl-4′-oxo-piperidin-2′-yl)-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-oxazolidine (11b). A solution of the 9:1 mixture **10a/10b** (1.20 g, 3.09 mmol) in MeOH (30 mL) was hydrogenated at 50 psi with $Pd(OH)_2$ (100 mg) in a Parr apparatus at 25°C. After 20 h, the catalyst was removed by filtration through Celite and the solvent evaporated. The crude oily residue (0.90 g) was dissolved in a 5:1 THF/H_2O mixture (30 mL) and treated with $Na_2CO_3{\cdot}10H_2O$ (1.14 g, 4 mmol) and benzylchloroformate (0.68 g, 4 mmol). After being stirred for 16 h at room temperature, the reaction mixture was diluted with brine (20 mL) and extracted with EtOAc (2×20 mL). Evaporation of the dried organic extracts furnished an oil that was purified by flash chromatography (eluent: ether/light petroleum 2:1) affording the title compound **11a** (1.07 g, 80%) as an oil. LRMS (EI): found 432.3; $C_{23}H_{32}N_2O_6$ requires 432.2. [Found: C, 63.80; H, 7.39. $C_{23}H_{32}N_2O_6$ requires C, 63.87; H, 7.46%]. $[\alpha]_D^{20}$=+30.5 (*c* 0.95, $CHCl_3$). ν_{max} (liquid film) 1715, 1680 cm^{-1}; δ_H (300 MHz, DMSO-d_6, 160°C) 1.40 (9H, s, 3*Me*), 1.45 (3H, s, *Me*), 1.57 (3H, s, *Me*), 2.38–2.45 (2H, m, CH_2CO), 2.52–2.68 (2H, m, COCH_2), 3.56–3.75 (1H, m, C$H_a$$H_b$O), 3.80–3.98 (2H, m, CH_2NCbz), 4.05–4.30 (2H, m, $CH_a$$H_b$O and *CH*NBoc), 4.54–4.64 (1H, m, *CH*NCbz), 5.15 (2H, *J*=12.0 Hz, AB system, OCH_2Ph), 7.23–7.42 (5H, m, arom.), and the title compound **11b** (0.14 g, 10%) as an oil. LRMS (EI): found 432.1; $C_{23}H_{32}N_2O_6$ requires 432.2. [Found: C, 63.80; H, 7.39. $C_{23}H_{32}N_2O_6$ requires C, 63.87; H, 7.46%]. $[\alpha]_D^{20}$=+9.5 (*c* 0.82, $CHCl_3$). ν_{max} (liquid film) 1715, 1680 cm^{-1}; δ_H (300 MHz, DMSO-d_6, 120°C) 1.32 (3H, s, *Me*), 1.36 (3H, s, *Me*), 1.45 (9H, s, 3*Me*), 2.38–2.46 (2H, m, CH_2CO), 2.52–2.58 (2H, m, COCH_2), 3.80–3.95 (3H, m, C$H_a$$H_bO, CH_2$NCbz), 4.11–4.20 (2H, m, $CH_a$$H_b$O, C*H*NBoc), 4.50–4.55 (1H, m, C*H*NCbz), 5.19 (2H, *J*=16 Hz, AB system, OCH_2Ph), 7.25–7.42 (5H, m, arom.).

4.1.4. (6*S*)-7-(*tert*-Butyldimethylsilyloxy)-6-(*tert*-butoxycarbonylamino)-1-(*p*-toluensulfonyl)-4-hepten-3-one (9). A mixture of **5**[7] (1.70 g, 3.50 mmol) and **7** (1.06 g, 3.50 mmol) in dry $CHCl_3$ (10 mL) was stirred at 25°C for 30 h, then concentrated in vacuo and the residue purified by flash chromatography (eluent: EtOAc/cyclohexane 1:2) affording the title compound **9** (1.43 g, 80%) as an oil. LRMS (EI): found 511.0; $C_{25}H_{41}NO_6SSi$ requires 511.2. [Found: C, 58.60; H, 7.99. $C_{25}H_{41}NO_6SSi$ requires C, 58.67; H, 8.08%]. $[\alpha]_D^{20}$=−7.2 (*c* 0.50, $CHCl_3$). ν_{max} (liquid film) 3300, 1690, 1680, 1625, 1590 cm^{-1}; δ_H (200 MHz, $CDCl_3$, 25°C) 0.06 (6H, s, Me_2Si), 0.89 (9H, s, Me_3CSi), 1.44 (9H, s, Me_3C), 2.44 (3H, s, Ph*Me*), 3.10 (2H, t, *J*=8.8 Hz, CH_2SO_2), 3.39 (2H, t, *J*=8.8 Hz, CH_2CO), 3.60–3.85 (2H, m, CH_2OSi), 4.40 (1H, m, C*H*NHBoc), 4.95 (1H, br d, *J*=7.0 Hz, NH), 6.20 (1H, dd, *J*=15.9, 1.8 Hz, HC=C*H*–CO), 6.80 (1H, dd, *J*=15.9, 5.5 Hz, *H*C=CH–CO), 7.38 (2H, d, *J*=8.0 Hz, arom.), 7.80 (2H, d, *J*=8.0 Hz, arom.).

4.1.5. (1*S*,2′*R*)-(1′-Benzyl-4′-oxo-piperidin-2′-yl)-2-(*tert*-butyldimethylsilyloxyethyl)carbamic acid *tert*-butyl ester (12a) and (1*S*,2′*S*)-(1′-benzyl-4′-oxo-piperidin-2′-yl)-2-(*tert*-butyldimethylsilyloxyethyl)carbamic acid *tert*-butyl ester (12b). Benzylamine (0.56 g, 5.24 mmol) was added to a solution of compound **9** (1.34 g, 2.62 mmol) in THF (7 mL), the reaction mixture stirred at 0°C for 5 days, then concentrated in vacuo. The residual oil was dissolved in EtOAc (20 mL), washed with $NaHCO_3$ solution (2×20 mL, sat. aq.) and brine (2×20 mL). The dried organic extracts were concentrated and the residue purified by flash chromatography (eluent: EtOAc/cyclohexane 1:3) affording the oily mixture of the title compounds **12a** and **12b** (0.85 g, 70%) in 1:5 ratio (HPLC analysis). A pure fraction of **12b** could be obtained and characterized. LRMS (EI): found 462.1; $C_{25}H_{42}N_2O_4Si$ requires 462.3. [Found: C, 64.81; H, 9.09. $C_{25}H_{42}N_2O_4Si$ requires C, 64.89; H, 9.15%]. $[\alpha]_D^{20}$= −9.4 (*c* 0.33, $CHCl_3$). ν_{max} (liquid film) 3250, 1710, 1680 cm^{-1}; δ_H (200 MHz, $CDCl_3$, 25°C) 0.05–0.07 (6H, m, Me_2Si), 0.82–0.87 (9H, m, Me_3CSi), 1.40–1.45 (9H, m, Me_3C), 1.80–2.45 (4H, m, CH_2COCH_2), 2.80–3.40 (4H, m, C*H*NCH_2, PhC$H_a$$H_b$N), 3.40–3.85 (3H, m, C$H_2OSi, PhCH_a$$H_b$N), 3.90–4.01 (1H, m, C*H*NHBoc), 5.20 (1H, br, *J*=7.0 Hz, NH), 7.20–7.40 (5H, m, arom).

4.1.6. (1*S*,2′*R*)-(1′-Benzyloxycarbonyl-4′-oxo-piperidin-2′-yl)-2-(*tert*-butyldimethylsilylethyl)carbamic acid *tert*-butyl ester (13a) and (1*S*,2′*S*)-(1′-benzyloxycarbonyl-4′-oxo-piperidin-2′-yl)-2-(*tert*-butyldimethylsilylethyl)carbamic acid *tert*-butyl ester (13b). A solution of piperidones **12a** and **12b** (1.00 g, 2.16 mmol) in MeOH (30 mL) was hydrogenated at 50 psi with $Pd(OH)_2$ (100 mg) in a Parr apparatus at 25°C. After 20 h the reaction mixture was filtered through Celite and the solvent evaporated. The residual oil was dissolved in a 5:1 mixture THF/H_2O (25 mL) and treated with $Na_2CO_3{\cdot}10H_2O$ (0.65 g, 2.28 mmol) and benzylchloroformate (0.39 g, 2.28 mmol). After being stirred for 12 h at room temperature, the mixture was diluted with brine (30 mL) and extracted with EtOAc (2×20 mL). Evaporation of the dried organic extracts and purification of the oily residue by flash chromatography (eluent: EtOAc/cyclohexane 1:3) afforded the title compound **13a** (0.20 g, 18%) as an oil. LRMS (EI): found 506.5; $C_{26}H_{42}N_2O_6Si$ requires 506.3. [Found: C, 61.59; H, 8.30; $C_{26}H_{42}N_2O_6Si$ requires C, 61.63; H, 8.35%]. $[\alpha]_D^{20}$=+25.3 (*c* 0.07, $CHCl_3$). ν_{max} (liquid film) 3250, 1710, 1680 cm^{-1}; δ_H (300 MHz, DMSO-d_6, 120°C) 0.05 (6H, s, Me_2Si), 0.85 (9H, m, Me_3CSi), 1.38 (9H, m, Me_3C), 2.37 (1H, dt, *J*=16.0, 5.0 Hz, HC*H*CO), 2.43 (1H, dd, *J*=10.0, 5.0 Hz, *H*CHCO), 2.52 (1H, dd, *J*=10.0, 5.0 Hz, HC*H*CO), 2.68 (1H, dd, *J*=16.0, 7.8 Hz, *H*CHCO), 3.48 (1H, ddd, *J*=14.0, 11.5, 5.1 Hz, *H*CHNCbz), 3.62–3.75 (3H, m, CH_2OSi, HC*H*NCbz), 4.15–4.24 (1H, m, C*H*NHBoc), 4.52–4.62 (1H, m, C*H*NCbz), 5.17 (2H, s, OCH_2Ph), 5.40–5.51 (1H, br, NH), 7.25–7.42 (5H, m, arom.), and the title compound **13b** (0.79 g, 72%) as an oil. LRMS (EI): found 506.2; $C_{26}H_{42}N_2O_6Si$ requires 506.3. [Found: C, 61.59; H, 8.30; $C_{26}H_{42}N_2O_6Si$ requires C, 61.63; H, 8.35%]. $[\alpha]_D^{20}$=−13.0 (*c* 0.23, $CHCl_3$). ν_{max} (liquid film) 3250, 1710, 1680 cm^{-1}; δ_H (300 MHz, DMSO-d_6, 120°C) 0.06 (6H, s, Me_2Si), 0.87 (9H, m, Me_3CSi), 1.40 (9H, m, Me_3C), 2.30–245 (3H, m, HC*H*CO, CH_2CO), 2.64 (1H, dd, *J*=16.5, 6.8 Hz, *H*CHCO), 3.40–3.85 (4H, m, CH_2NCbz, CH_2OSi), 4.20–4.30 (1H, m, C*H*NHBoc), 4.65–4.78 (1H, m, C*H*NCbz), 5.24 (2H, *J*=15.5 Hz, AB system, OCH_2Ph), 6.05 (1H, br, NH) 7.25–7.42 (5H, m, arom.).

4.1.7. (1*S*,2′*R*)-1-(1′-Benzyloxycarbonyl-4′-oxo-piperidin-2′-yl)-2-(hydroxyethyl)carbamic acid *tert*-butyl ester (14a) and (1*S*,2′*S*)-1-(1′-benzyloxycarbonyl-4′-oxo-piperidin-2′-yl)-2-(hydroxyethyl)carbamic acid-*tert*-butyl ester (14b). *Method A*. A solution of **11a** (0.46 g, 1.06 mmol) in acetic acid (4 mL) containing H_2O (1 mL) was stirred at room temperature for 32 h, then evaporated in vacuo. The residue was dissolved in EtOAc (10 mL) and washed with $NaHCO_3$ solution (10 mL, sat. aq.). Evaporation of the dried organic extracts afforded the title compound **14a** (0.40 g, 97%) as an oil.

Method B. A solution of **13a** (0.16 g, 0.31 mmol) and tetrabutylammonium fluoride trihydrate (0.39 g, 1.24 mmol) in THF (5 mL) was stirred at room temperature overnight, then the solvent was evaporated under reduced pressure. The residual oil was dissolved in EtOAc (20 mL) and washed with water (2×20 mL). Evaporation of the dried organic extracts gave the title compound **14a** as an oil (0.11 g, 94%), which was pure enough to be used in the next step without purification.

In both cases, a sample was purified by flash chromatography (eluent: EtOAc/cyclohexane 1:1) for analytical purposes. LRMS (EI): found 392.3; $C_{20}H_{28}N_2O_6$ requires 392.2. [Found: C, 61.12; H, 7.14. $C_{20}H_{28}N_2O_6$ requires C, 61.21; H, 7.19%]. $[\alpha]_D^{20}=+27.7$ (*c* 1.64, $CHCl_3$). ν_{max} (liquid film) 3450, 1715, 1680 cm^{-1}; δ_H (300 MHz, DMSO-d_6, 120°C) 1.40 (9H, s, 3*Me*), 2.38–2.58 (2H, m, CH_2CO), 2.51–2.72 (2H, m, COCH_2), 3.38–3.65 (4H, m, CH_2OH, CH_2NCbz), 4.08–4.20 (1H, m, C*H*NHBoc), 4.55–4.65 (1H, m, C*H*NCbz), 5.19 (2H, s, OCH_2Ph), 5.62–5.78 (1H, br, NH), 7.25–7.42 (5H, m, arom.).

The same procedures were applied to **12b** and **13b** to give **14b**. LRMS (EI): found 392.1; $C_{20}H_{28}N_2O_6$ requires 392.2. [Found: C, 61.12; H, 7.14. $C_{20}H_{28}N_2O_6$ requires C, 61.21; H, 7.19%]. $[\alpha]_D^{20}=-21.8$ (*c* 0.82, $CHCl_3$). ν_{max} (liquid film) 3450, 1715, 1680 cm^{-1}; δ_H (300 MHz, DMSO-d_6, 120°C) 1.42 (9H, s, Me_3C), 2.40–2.55 (2H, m, CH_2CO), 2.60–2.82 (2H, m, COCH_2), 3.40–3.65 (4H, m, CH_2OH, CH_2NCbz), 4.18–4.22 (1H, m, C*H*NHBoc), 4.70–4.78 (1H, m, C*H*NCbz), 5.20 (2H, *J*=15.9 Hz, AB system, OCH_2Ph), 5.62–5.78 (1H, br, NH), 7.25–7.42 (5H, m, arom.).

4.1.8. (2*S*,2′*R*)-*tert*-Butoxycarbonylamino-(4′-oxo-piperidin-2′-yl)-acetic acid (15). To a stirred and cooled (0°C) solution of the alcohol **14a** (0.40 g, 1.02 mmol) in acetone (20 mL), Jones reagent (2 mL) was added dropwise. After being stirred for 2 h at 0°C and 3 h at room temperature, the excess of oxidant was destroyed with 2-propanol (10 mL). The reaction mixture was dried, filtered trough Celite and concentrated in vacuo. The residual oil was dissolved in $CHCl_3$ (20 mL), washed with water (2×10 mL) and the organic extracts were dried and evaporated. Purification of the residue by flash chromatography (eluent: EtOAc containing 0.1% acetic acid) afforded the title compound **15** (0.34 g, 83%) as a colorless oil. LRMS (EI): found 406.1; $C_{20}H_{26}N_2O_7$ requires 406.2. [Found: C, 59.03; H, 6.39. $C_{20}H_{26}N_2O_7$ requires C, 59.10; H, 6.45%]. $[\alpha]_D^{20}=+16.1$ (*c* 2.28, MeOH) (lit.[6] $[\alpha]_D^{20}=+16.0$ (*c* 0.84, MeOH)). ν_{max} (liquid film) 3450, 1715, 1680 cm^{-1}; δ_H (300 MHz, DMSO-d_6, 120°C) 1.39 (9H, s, 3*Me*), 2.36 (1H, dt, *J*=15.8, 4.9 Hz, HC*H*CO), 2.44 (1H, dd, *J*=10.5, 7.8 Hz, *H*CHCO), 2.54 (1H, dd, *J*=10.5, 3.5 Hz, HC*H*CO), 2.68 (1H, dd, *J*=15.8, 6.84 Hz, *H*CHCO) 3.40–3.65 (2H, m, CH_2NCbz), 4.08–4.20 (1H, m, C*H*NHBoc), 4.55–4.65 (1H, m, C*H*NCbz), 5.15 (2H, s, OCH_2Ph), 5.62–5–78 (1H, d, *J*=8.0 Hz, NH) 7.25–7.42 (5H, m, arom.).

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