γ-Substituted pyrrole-based silyl dienol ethers as α-amino acid enolate equivalents: a versatile entry to racemic α-substituted α-amino acids

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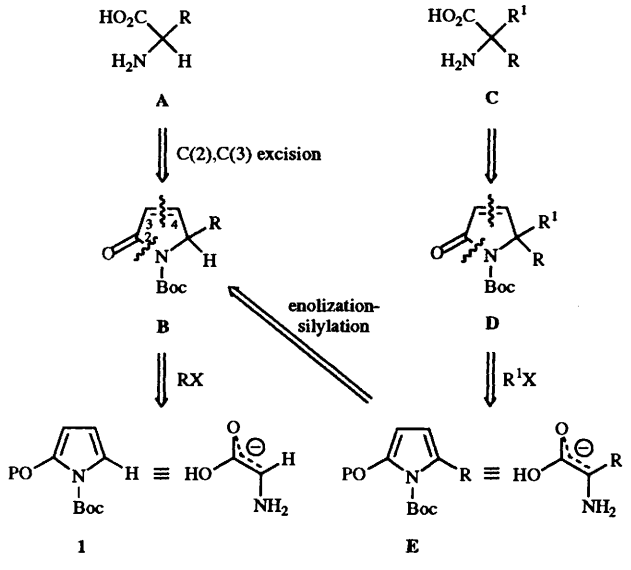
γ-Substituted siloxypyrrole derivatives **5**–**7** have been synthesized by direct alkylation of *N*-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)pyrrole **1**. These underwent subsequent alkylation with alkyl halides or aldehydes to produce γ,γ-disubstituted α,β-unsaturated lactam intermediates in good yields. Oxidative cleavage of the C(3)–C(4) bond within the lactam moiety gave rise to a number of α-substituted α-amino acids. These include racemic α-methylphenylalanine **14**, α-benzylphenylalanine **15**, α-benzylserine **18** and α-methylthreonine **21**.

Research in our laboratories has recently focused on the exploitation of *N*-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)pyrrole **1**, quickly available from pyrrole, for syntheses of a variety of racemic and homochiral α-amino acids.[1] It was envisaged (Scheme 1) that amino acids of type **A** could be



Scheme 1 P = *tert*-butyldimethylsilyl; Boc = *tert*-butoxycarbonyl

generated from γ-substituted α,β-unsaturated lactams of type **B** *via* oxidative extrusion of C-2 and C-3. Compounds **B** were, in turn, obtained by direct alkylation of **1** with appropriate electrophilic reactants RX. The enol ether **1** can be viewed as a masked glycine enolate equivalent.

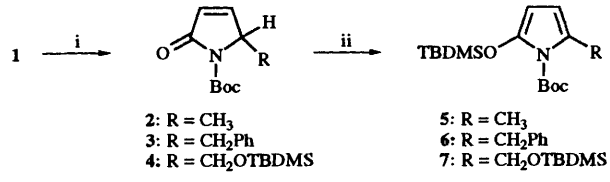
Further exploring the potential of pyrrole-based silyl dienol ethers for the assembly of biologically important molecules and conjugates,[1,2] we reasoned that exploitation of γ-substituted dienol ethers of general formula **E**, obtainable from **B** *via* enolization-silylation, would provide access to α-substituted α-amino acids of type **C** *via* the intermediacy of γ,γ-disubstituted lactams **D**. Hence, intermediates **E** can be envisioned as α-amino acid enolate equivalents.

Given the importance of α-substituted α-amino acids as enzyme inhibitors[3] and as conformational modifiers in physiologically active peptides,[4] the design and implementation of novel synthetic strategies to access them from readily available precursors is of much current interest.[5] This paper describes the syntheses of certain α-branched α-amino acids, including α,α-dialkyl derivatives **14** and **15** and β-hydroxylated congeners **18** and **21**.

Results and discussion

Synthesis of γ-substituted dienol ether precursors

Methyl-, benzyl- and hydroxymethyl-substituted precursors **5**–**7** could be prepared by regiospecific alkylation of **1** at the γ-position followed by enolization-silylation of the lactams so formed. For alkyl-substituted compounds **5** and **6**, **1** was subjected to Lewis acid-mediated alkylation with methyl iodide and benzyl bromide, respectively. $SnCl_4$, $BF_3{\cdot}OEt_2$ and silver trifluoroacetate were tried as Lewis acids. The last-mentioned proved to be superior providing the lactams **2** and **3** in 65 and 70% yields, respectively (Scheme 2).



Scheme 2 *Reagents and conditions:* i, for **2**, CH_3I, CF_3CO_2Ag, CH_2Cl_2, 0 °C; for **3**, $PhCH_2Br$, CF_3CO_2Ag, CH_2Cl_2, 0 °C; for **4**, CH_2O (gas), $SnCl_4$, Et_2O, −80 °C; ii, TBDMSOTf, 2,6-dimethylpyridine, CH_2Cl_2, 20 °C

Our experience with **1**[1,2] led us to adopt the same silyl dienol ether-forming protocol to generate γ-substituted analogues **5** and **6**. Thus, treatment of **2** and **3** with *tert*-butyldimethylsilyltrifluoromethane sulfonate in the presence of 2,6-dimethylpyridine resulted in clean enolization at C-5, leading to **5** and **6** in 92 and 96% yields, respectively. For the hydroxymethyl-substituted analogue **7**, direct hydroxymethylation of **1** with anhydrous formaldehyde was attempted. Indeed, exposure of **1** to formaldehyde in diethyl ether in the presence of 1.2 equiv. of $SnCl_4$ at −80 °C resulted in formation of the expected silyl-protected lactam **4** in a good 60% yield. Silyl ether formation was carried out following exactly the above procedure for **5** and **6**, providing **7** in almost quantitative yield.

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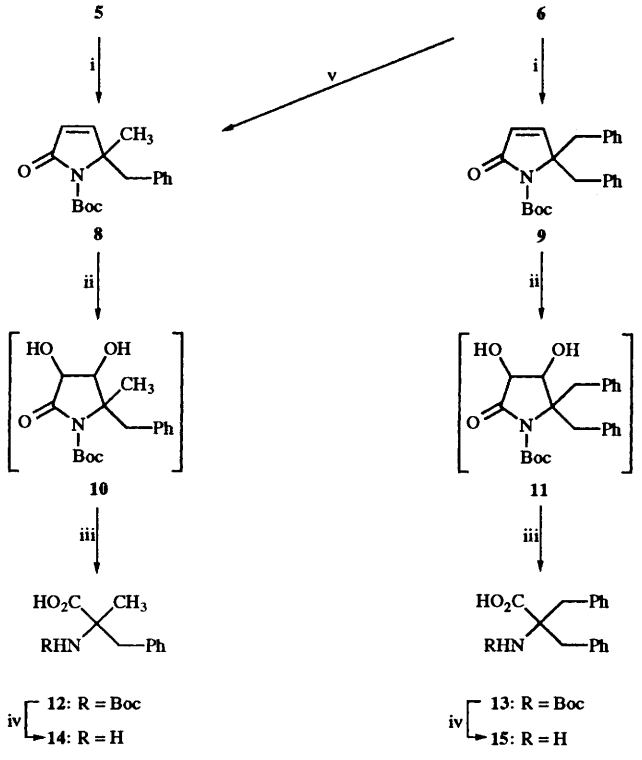
Synthesis of α,α-dialkyl-α-amino acids

With a practical preparation of γ-substituted silyl dienol ethers secured, we then proceeded to use these novel nucleophiles to synthesize two representative compounds, namely, racemic α-methylphenylalanine **14** and α-benzylphenylalanine **15**. Our alkylation-excision protocol previously developed for syntheses of a series of α-unsubstituted α-amino acids[1] was adopted here as an approach to α-alkyl-substituted congeners **14** and **15**. As shown in Scheme 3, silver trifluoroacetate-promoted coupling



Scheme 3 *Reagents and conditions:* i, $PhCH_2Br$, CF_3CO_2Ag, CH_2Cl_2, 0 °C; ii, $KMnO_4$, dicyclohexano-18-crown-6 ether, CH_2Cl_2, 20 °C; iii, LiOH, THF, 0 °C; then aq. $NaIO_4$, SiO_2, CH_2Cl_2, 20 °C; then $NaIO_4$, RuO_2, CCl_4–MeCN-aq. acetone; iv, HCl, THF, 20 °C; then SiO_2, chromatogr., CH_2Cl_2–MeOH–aq. NH_4OH; v, MeI, CF_3CO_2Ag, CH_2Cl_2, 0 °C

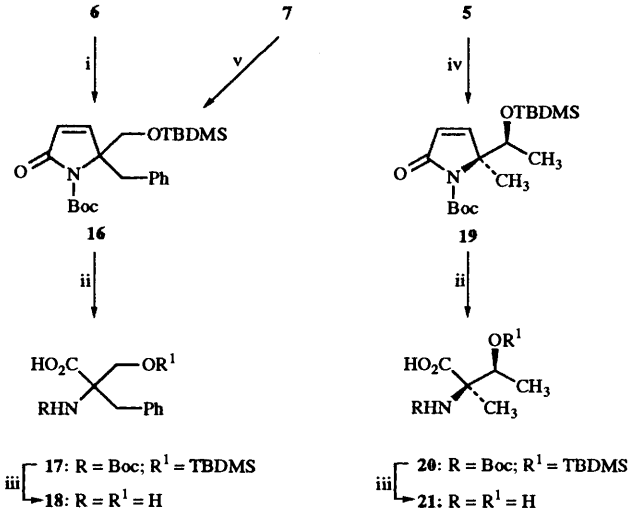
of **5** and **6** with benzyl bromide indeed led to formation of γ,γ-disubstituted unsaturated lactams **8** and **9** in reasonably good yields (60 and 65%).

Dihydroxylation of the double bond in **8** and **9** using $KMnO_4$ under solid–liquid phase-transfer conditions gave rise to the hydroxylated lactams **10**‡ and **11**, which were directly converted into *N*-Boc-protected α-amino acids **12** and **13** by three sequential operations comprising hydrolytic lactam opening (LiOH, THF), oxidative fission of the vicinal diol ($NaIO_4$) and further oxidation of the carbaldehyde compounds ($NaIO_4$, RuO_2) formed. Thus, avoiding isolation of any intermediary compounds, **12** and **13** were obtained in 51 and 54% isolated yields based on the respective precursors **8** and **9**. Finally, removal of the *tert*-butoxycarbonyl group with aqueous HCl in THF followed by ammonia neutralization and flash chromatographic purification generated the free amino acids **14** and **15** in 89 and 91% yields, respectively.

A salient feature of this approach is that two different ways of access to a given unsymmetrical amino acid can be envisioned depending upon the availability of the silyl enol ether precursor and the reactivity and bulkiness of the electrophilic reactant. Thus, for example, the synthesis of **14** was alternatively planned *via* alkylation of benzyl-substituted enol ether **6** with methyl iodide. In the event, the lactam **8** was prepared (66% yield) which was then elaborated into **14** by the above disclosed set of reactions.

Synthesis of α-substituted-β-hydroxy-α-amino acids

Our previous experience with the $SnCl_4$-catalysed coupling of **1** with aldehyde compounds[1,2] encouraged application of the same reaction protocol to γ-substituted analogues **5** and **6** (Scheme 4). As hoped, hydroxymethylation of **6** with



Scheme 4 *Reagents and conditions:* i, CH_2O (gas), $SnCl_4$, Et_2O, −80 °C; then TBDMSCl, imidazole, DMF; ii, $KMnO_4$, dicyclohexano-18-crown-6, CH_2Cl_2; then aq. LiOH, THF, 0 °C; then aq. $NaIO_4$, SiO_2, CH_2Cl_2, 20 °C; then $NaIO_4$, RuO_2, CCl_4-MeCN-aq. acetone; iii, HCl, THF; then SiO_2, chromatogr., CH_2Cl_2–MeOH–aq. NH_4OH; iv, MeCHO, $SnCl_4$, Et_2O, −80 °C; then TBDMSCl, imidazole, DMF; v, $PhCH_2Br$, CF_3CO_2Ag, CH_2Cl_2, 0 °C

formaldehyde followed by silylation afforded the γ,γ-disubstituted lactam **16** (55% yield) which, upon sequential dihydroxylation, oxidative sacrifice of the C-2 and C-3 carbon atoms and deprotective work-up, yielded racemic α-benzylserine **18** in a useful 38% overall yield for the entire sequence from **16**. As for α-methylphenylalanine **14**, the alternate approach to **18** involved silver trifluoroacetate-promoted coupling of benzyl bromide to the hydroxymethylated silylenol ether **7**, and this led to **16**, the key synthetic precursor of **18**, in 58% yield.

Access to α-methylthreonine **21** dictated the choice of methyl-substituted derivative **5**, an alanine enolate equivalent, and acetaldehyde as requisite precursors. As expected, the $SnCl_4$-catalysed aldol condensation proved diastereoselective providing, after silylation, 4,5-*threo*-configurated lactam **19** as predominant diastereoisomer (>95% d.e.) in 51% isolated yield. Conversion of **19** into racemic α-methylthreonine **21** occurred without incident by following the same procedure as that used for **14**, **15** and **18**. Thus, the crystalline amino acid **21** was obtained (36% yield from **19**) whose physical and spectral characteristics matched the reported values for the homochiral counterparts.[5g]

Conclusions

The easy synthesis of γ-substituted siloxypyrrole derivatives **5**–**7** coupled with the possibility of utilizing them as masked α-amino acid enolate equivalents allowed us to prepare some important α-alkyl-α-amino acids including the phenylalanine

‡ It should be noted that, though irrelevant to the preparation of amino acids here described, the dihydroxylation proceeds with almost complete diastereocontrol as judged from ^1H and ^{13}C NMR spectra of the diol intermediate formed.

derivatives **14** and **15**, serine **18** and threonine **21**. Remarkably, when prochiral aldehyde acceptors were involved (*e.g.* acetaldehyde) the carbon–carbon bond formation proved highly diastereoselective rendering important β-hydroxylated α-substituted-α-amino acids (*e.g.* **21**) available by synthesis. Future goals include expansion of this tactic to preparation of diverse α-substituted α-amino acid congeners and the development of an asymmetric version of this methodology en route to enantiomerically pure compounds.

Experimental

Mps were determined on an Electrothermal apparatus and are recorded uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 or Bruker AC-100 instrument. *J* Values are given in Hz, and chemical shifts are referenced to tetramethylsilane (δ 0.0), DOH (δ 4.80), or CD_3OD (δ_H 3.35 and δ_C 49.0). Chemical ionization mass spectra were measured on a Finnigan Mat SSQ710 spectrometer. TLC was carried out on Merck Kieselgel 60 F_{254} glass-backed plates. Silica gel (particle size 70–230 mesh) supplied by Merck was employed for flash chromatography. Elemental analyses were performed by the Microanalytical Laboratory of the University of Sassari. *N*-(*tert*-Butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)pyrrole **1** was prepared from pyrrole according to a described protocol.[2a,e]

(±)-1-(*tert*-Butoxycarbonyl)-5-methyl-2,5-dihydropyrrol-2-one 2

Typical procedure. To a solution of **1** (1.0 g, 3.4 mmol) in dry CH_2Cl_2 (15 cm^3) under nitrogen was added methyl iodide (0.42 cm^3, 6.7 mmol), and the mixture was cooled at 0 °C. Silver trifluoroacetate (1.48 g, 6.7 mmol) was added to the mixture which was then stirred for 2 h. After ambient temperature was reached, the reaction was quenched by addition of saturated aq. $NaHCO_3$ to the mixture which was then extracted with Et_2O (3 × 10 cm^3). The combined extracts were evaporated and the residue purified by flash chromatography on silica gel eluting with hexane–EtOAc (60:40) to afford the pure dihydropyrrolone **2** (0.44 g, 65%) as a *white waxy solid* (C, 61.2; H, 7.7; N, 6.9. $C_{10}H_{15}NO_3$ requires C, 60.9; H, 7.7; N, 7.1%); δ_H(300 MHz; $CDCl_3$) 1.45 (3 H, d, *J* 6.7, Me), 1.57 (9 H, s, Bu^t), 4.63 (1 H, tq, *J* 6.7 and 1.8, 5-H), 6.06 (1 H, dd, *J* 6.1 and 1.7, 3-H) and 7.14 (1 H, dd, *J* 6.1 and 1.9, 4-H); δ_C(75.4 MHz; $CDCl_3$) 18.1, 28.1 (3 C), 58.4, 82.7, 125.7, 150.3, 151.9 and 169.0.

(±)-5-Benzyl-1-(*tert*-butoxycarbonyl)-2,5-dihydropyrrol-2-one 3. The title compound was prepared by starting with **1** (1.0 g, 3.4 mmol) and benzyl bromide (0.8 cm^3, 6.7 mmol) and following the procedure described for compound **2**, to give **3** as a *white crystalline solid* (0.65 g, 70%), mp 103–105 °C (Found: C, 70.0; H, 6.9; N, 5.3. $C_{16}H_{19}NO_3$ requires C, 70.3; H, 7.0; N, 5.1%); δ_H(300 MHz; $CDCl_3$) 1.62 (9 H, s, Bu^t), 2.78 (1 H, dd, *J* 13.1 and 9.2, CH_2Ph), 3.50 (1 H, dd, *J* 13.1 and 3.9, CH_2Ph), 4.74 (1 H, dq, *J* 9.2 and 1.8, 5-H), 5.97 (1 H, dd, *J* 6.1 and 1.2, 3-H), 7.03 (1 H, dd, *J* 6.1 and 1.8, 4-H), 7.12 (2 H, m, ArH) and 7.27 (3 H, m, ArH); δ_C(25.2 MHz; $CDCl_3$) 28.2 (3 C), 38.4, 63.3, 83.0, 126.5, 127.1, 128.6 (2 C), 129.4 (2 C), 135.4, 149.4, 150.1 and 169.1.

(±)-1-(*tert*-Butoxycarbonyl)-5-(*tert*-butyldimethylsiloxymethyl)-2,5-dihydropyrrol-2-one 4. To a stirred solution of compound **1** (1.0 g, 3.4 mmol) in Et_2O (20 cm^3) cooled at −80 °C was added $SnCl_4$ (0.8 cm^3, 6.7 mmol) under nitrogen. A stream of gaseous formaldehyde, obtained by thermal depolymerization of solid paraformaldehyde (0.4 g, 13.5 mmol), was passed throughout the resulting slurry using nitrogen as a carrier, the temperature being maintained at −80 °C for 2 h. After this, the reaction was quenched by addition of saturated aq. $NaHCO_3$ to the reaction mixture which was then extracted with EtOAc (3 × 15 cm^3). The combined extracts were evaporated and the crude product was purified by flash chromatography on silica gel eluting with hexane–EtOAc (70:30) to afford the pyrrolidinone **4** as a *white solid* (0.67 g, 60%), mp 44–48 °C (Found: C, 58.5; H, 8.8; N, 4.5. $C_{16}H_{29}NO_4Si$ requires C, 58.7; H, 8.9; N, 4.3%); δ_H(300 MHz; $CDCl_3$) −0.19 (3 H, s, Me), −0.01 (3 H, s, Me), 0.81 (9 H, s, Bu^t), 1.50 (9 H, s, Bu^t), 3.67 (1 H, dd, *J* 9.7 and 6.7, 6-H^a), 4.09 (1 H, dd, *J* 9.7 and 3.6, 6-H^b), 4.55 (1 H, dddd, *J* 6.7, 3.6, 1.9 and 1.7, 5-H), 6.07 (1 H, dd, *J* 6.1 and 1.7, 3-H) and 7.21 (1 H, dd, *J* 6.1 and 1.9, 4-H); δ_C(75.4 MHz; $CDCl_3$) −5.6, −5.5, 18.0, 25.6 (3 C), 28.1 (3 C), 62.4, 63.5, 82.8, 127.0, 149.6, 153.1 and 169.2.

1-(*tert*-Butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)-5-methylpyrrole 5

Typical procedure. To a solution of the lactam **2** (0.36 g, 1.8 mmol) in anhydrous CH_2Cl_2 (18 cm^3) were added 2,6-dimethylpyridine (0.64 cm^3, 5.5 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) (0.42 cm^3, 1.8 mmol) under argon at room temperature. After being stirred for 1 h, the mixture was evaporated and the residue flash chromatographed on silica gel eluting with hexane–EtOAc (60:40) to give pure silyl ether **5** as a *pale yellow oil* (0.52 g, 92%) (Found: C, 61.5; H, 9.6; N, 4.3. $C_{16}H_{29}NO_3Si$ requires C, 61.7; H, 9.4; N, 4.5%); δ_H(300 MHz; $CDCl_3$) 0.24 (6 H, s, Me), 0.90 (9 H, s, Bu^t), 1.59 (9 H, s, Bu^t), 2.27 (3 H, m, 5-H), 5.10 (1 H, m, 3-H) and 5.61 (1 H, m, 4-H); δ_C(75.4 MHz; $CDCl_3$) −5.0, −3.1, 15.9, 18.2, 25.6 (3 C), 27.9 (3 C), 81.9, 89.9, 107.1, 121.9, 142.7 and 148.9.

5-Benzyl-1-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)-pyrrole 6. The title compound, prepared from compound **3** (0.8 g, 3.2 mmol) by following the procedure described for compound **5**, was obtained as a *white glassy solid* (1.2 g, 96%) (Found: C, 68.0; H, 8.8; N, 3.3. $C_{22}H_{33}NO_3Si$ requires C, 68.2; H, 8.6; N, 3.6%); δ_H(300 MHz; $CDCl_3$) 0.19 (6 H, s, Me), 0.96 (9 H, s, Bu^t), 1.30 (9 H, s, Bu^t), 4.02 (2 H, s, CH_2Ph), 5.12 (1 H, d, *J* 3.6, 3-H), 5.57 (1 H, d, *J* 3.6, 4-H), 7.03 (2 H, m, ArH) and 7.16 (3 H, m, ArH); δ_C(25.2 MHz; $CDCl_3$) −4.7 (2 C), 18.4, 25.9 (3 C), 27.7 (3 C), 35.5, 83.1, 90.4, 109.3, 124.1, 126.0, 128.3 (5 C), 143.6 and 148.9.

1-(*tert*-Butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)-5-(*tert*-butyldimethylsiloxymethyl)pyrrole 7. The title compound, prepared from compound **4** (0.5 g, 1.5 mmol) by following the procedure described for **5**, was obtained as an *oil* (0.65 g, 98%) (Found: C, 60.0; H, 9.6; N, 2.9. $C_{22}H_{43}NO_4Si_2$ requires C, 59.8; H, 9.8; N, 3.2); δ_H(300 MHz; $CDCl_3$) 0.00 (6 H, s, Me), 0.01 (6 H, s, Me), 0.86 (9 H, s, Bu^t), 0.87 (9 H, s, Bu^t), 1.56 (9 H, s, Bu^t), 4.67 (2 H, br s, 6-H), 5.13 (1 H, d, *J* 3.6, 3-H) and 5.83 (1 H, br d, *J* 3.5, 4-H); δ_C(75.4 MHz; $CDCl_3$) −5.2 (2 C), −4.8 (2 C), 18.1, 18.3, 25.7 (3 C), 25.8 (3 C), 27.9 (3 C), 60.1, 83.0, 90.3, 108.1, 125.6, 144.0 and 148.9.

(±)-5-Benzyl-1-(*tert*-butoxycarbonyl)-5-methyl-2,5-dihydropyrrol-2-one 8. The title compound, prepared by starting with **5** (0.3 g, 0.96 mmol) and benzyl bromide (1.1 cm^3, 9.6 mmol) by following the procedure described for the lactam **2**, was obtained as a *colourless oil* (0.17 g, 60%) (Found: C, 69.9; H, 7.6; N, 4.6. $C_{17}H_{21}NO_3$ requires C, 71.1; H, 7.4; N, 4.9%); δ_H(100 MHz; $CDCl_3$) 1.62 (3 H, s, Me), 1.63 (9 H, s, Bu^t), 3.10 (1 H, 1/2 AB q, *J* 13.5, 1/2 CH_2Ph), 3.46 (1 H, 1/2 AB q, *J* 13.5, 1/2 CH_2Ph), 5.85 (1 H, d, *J* 6.1, 3-H), 7.00 (1 H, d, *J* 6.1, 4-H) and 7.24 (5 H, m, ArH). Alternatively, the same compound was prepared from compound **6** (0.21 g, 0.58 mmol) and methyl iodide (0.36 cm^3, 5.8 mmol) by following the same protocol (109 mg, 66%).

5,5-dibenzyl-1-(*tert*-butoxycarbonyl)pyrrolin-2-one 9. The title compound, prepared from compound **6** (0.32 g, 0.87 mmol) and benzyl bromide (1.0 cm^3, 8.7 mmol) by following the procedure described for the lactam **2**, was obtained as a *white solid* (205 mg, 65%), mp 84–88 °C (Found: C, 76.2; H, 7.0; N, 3.7.

$C_{23}H_{25}NO_3$ requires C, 76.0; H, 6.9; N, 3.9%); δ_H(300 MHz; $CDCl_3$) 1.67 (9 H, s, Bu^t), 3.16 (2 H, 2 × 1/2 AB q, J 13.6, CH_2Ph), 3.68 (2 H, 2 × 1/2 AB q, J 13.6, CH_2Ph), 5.64 (1 H, d, J 6.1, 3-H), 6.98 (1 H, d, J 6.1, 4-H), 7.01 (4 H, m, ArH) and 7.18 (6 H, m, ArH); δ_C(75.4 MHz; $CDCl_3$) 28.2 (3 C), 41.9 (2 C), 72.0, 82.7, 125.6, 126.9 (2 C), 128.1 (4 C), 130.0 (4 C), 134.8 (2 C), 150.3, 153.7 and 168.6.

(±)-*N*-(*tert*-Butoxycarbonyl)-α-methylphenylalanine 12

Typical procedure. To a stirred solution of the lactam **8** (184 mg, 0.68 mmol) in anhydrous CH_2Cl_2 (4 cm^3) were added dicyclohexano-18-crown-6 ether (32 mg, 0.08 mmol) and powdered $KMnO_4$ (43 mg, 0.28 mmol) at room temperature. After 2 h, the reaction was quenched by addition of a saturated aqueous Na_2SO_3 and citric acid to the reaction mixture until the brown colour disappeared. The resulting colourless solution was extracted with ethyl acetate (3 × 10 cm^3) and the combined extracts were evaporated to give the crude diol **10** which was used as such in the next reaction. The diol was directly dissolved in THF (5 cm^3) and 1 mol dm^{-3} aq. LiOH (1.0 cm^3) was added to the stirred solution at 0 °C. After 15–30 min the solvent was removed and the residue was dissolved in CH_2Cl_2 (8 cm^3). SiO_2 (70-230 mesh, 4 g) was added to the solution and the resulting slurry was treated with 0.65 mol dm^{-3} aq. $NaIO_4$ (1.5 cm^3) at room temperature with vigorous stirring. After 15 min the slurry was filtered under suction and the silica was washed with CH_2Cl_2. The combined filtrate and washings were evaporated to give a residue which was directly dissolved in MeCN (1.1 cm^3)–CCl_4 (1.1 cm^3)–water (1.5 cm^3)–acetone (0.3 cm^3). Solid $NaIO_4$ (200 mg, 0.92 mmol) was then added to the solution followed by hydrated RuO_2 (20 mg). After the mixture had been stirred for 30 min at room temperature it was treated with propan-2-ol (5 cm^3) and filtered through a Celite pad. The filtrate was evaporated and the residue was chromatographed over silica gel eluting with a EtOAc–hexane (75:25) to give protected α-methylphenylalanine **12** (97 mg, 51% from **8**) as a *glassy solid* (Found: C, 64.3; H, 7.4; N, 4.8. $C_{15}H_{21}NO_4$ requires C, 64.5; H, 7.6; N, 5.0%); δ_H(300 MHz; CD_3OD) 1.44 (9 H, s, Bu^t), 1.52 (3 H, s, Me), 3.20 (1 H, 1/2 AB q, J 13.2, CH_2Ph), 3.30 (1 H, 1/2 AB q, J 13.2, CH_2Ph) and 7.17 (5 H, m, ArH); δ_C(75.4 MHz; CD_3OD) 24.9, 28.9 (3 C), 42.4, 62.0, 80.2, 127.2, 128.7 (2 C), 131.2 (2 C), 139.6, 151.1 and 170.2; m/z (CI, methane) 280 (M + H)$^+$.

***N*-(*tert*-Butoxycarbonyl)-α-benzylphenylalanine 13**. The title compound, prepared from the lactam **9** (146 mg, 0.43 mmol) by following the procedure described for **12**, was obtained as a *glass* (83 mg, 54% from **9**) (Found: C, 70.9; H, 7.3; N, 3.6. $C_{21}H_{25}NO_4$ requires C, 71.0; H, 7.1; N, 3.9%); δ_H(300 MHz; $CDCl_3$) 1.49 (9 H, s, Bu^t), 3.22 (2 H, 2 × 1/2 AB q, J 13.1, CH_2Ph), 3.79 (2 H, 2 × 1/2 AB q, J 13.1, CH_2Ph), 5.22 (1 H, br s, NH) and 7.21 (10 H, m, ArH); δ_C(25.2 MHz; $CDCl_3$) 28.5 (3 C), 41.2 (2 C), 66.3, 79.4, 126.6 (2 C), 128.2 (4 C), 129.9 (4 C), 136.5 (2 C), 154.4 and 177.2; m/z (CI, methane) 356 (M + H)$^+$.

(±)-α-Methylphenylalanine 14

Typical procedure. The protected amino acid **12** (97 mg, 0.27 mmol) was dissolved in THF (2 cm^3) and treated with 6 mol dm^{-3} aqueous HCl (2 cm^3) at room temperature. After being stirred for 2 h, the mixture was evaporated and the residue was subjected to flash chromatographic purification on silica gel, eluting with CH_2Cl_2–MeOH–30% aq. NH_4OH (7:3:1). Evaporation of the eluate furnished the amino acid **14** (43 mg, 89%) as a white powder, mp 290 °C (decomp.) [lit.,[6] 293–294 °C (decomp.)]; δ_H(300 MHz; CD_3OD) 1.52 (3 H, s, Me), 2.96 (1 H, 1/2 AB q, J 13.5, CH_2Ph), 3.27 (1 H, 1/2 AB q, J 13.5, CH_2Ph) and 7.28 (5 H, m, ArH); δ_C(75.4 MHz; CD_3OD) 23.3, 44.2, 60.5, 128.5, 129.7 (2 C), 131.3 (2 C), 135.9 and 173.8; m/z (CI, methane) 180 (M + H)$^+$. The ^{1}H and ^{13}C NMR data compared well with those reported for (*R*)-α-methylphenylalanine.[5h]

α-Benzylphenylalanine 15

The title compound, prepared from the protected amino acid **13** (83 mg, 0.23 mmol), was a *glassy solid* (53 mg, 91%) (Found: C, 75.1; H, 6.9; N, 5.3. $C_{16}H_{17}NO_2$ requires C, 75.3; H, 6.7; N, 5.5%); δ_H(300 MHz; CD_3OD) 3.31 (2 H, 2 × 1/2 AB q, J 14.1, CH_2Ph) and 3.45 (2 H, 2 × 1/2 AB q, J 14.1, CH_2Ph) and 7.32 (10 H, m, ArH); δ_C(75.4 MHz; CD_3OD) 43.0 (2 C), 66.1, 128.8 (2 C), 130.0 (4 C), 131.5 (4 C), 134.1 (2 C) and 179.3; m/z (CI, methane) 256 (M + H)$^+$.

(±)-5-Benzyl-*N*-(*tert*-butoxycarbonyl)-5-(*tert*-butyldinethylsiloxymethyl)-2,5-dihydropyrrol-2-one 16

The title compound was prepared from compound **6** (0.8 g, 2.1 mmol) and formaldehyde (0.5 g, 16.6 mmol) essentially according to the procedure described for **4**. The 5-hydroxymethyl derivative so obtained was then dissolved in dry dimethylformamide (7 cm^3) to which TBDMSCl (187 mg, 1.24 mmol) and imidazole (84 mg, 1.24 mmol) were added. After being stirred at room temperature for 20 h, the mixture was poured into 5% aqueous citric acid (8 cm^3), and the resulting solution was extracted with Et_2O (3 × 10 cm^3). The combined extracts were evaporated and the crude lactam **16** was purified by flash chromatography on silica gel eluting with hexane–EtOAc (70:30) to afford the pure lactam **16** (482 mg, 55%) as a *colourless oil* (Found: C, 66.0; H, 8.7; N, 3.1. $C_{23}H_{35}NO_4Si$ requires C, 66.2; H, 8.5; N, 3.4%); δ_H(300 MHz; $CDCl_3$) 0.04 (6 H, s, Me), 0.86 (9 H, s, Bu^t), 1.60 (9 H, s, Bu^t), 3.09 (1 H, 1/2 AB q, J 13.7, CH_2Ph), 3.47 (1 H, 1/2 AB q, J 13.7, CH_2Ph), 4.06 (2 H, AB q, J 9.6, $\Delta\nu$ 17.7, CH_2O), 5.85 (1 H, d, J 6.1, 3-H), 6.99 (2 H, m, ArH), 7.06 (1 H, d, J 6.1, 4-H) and 7.19 (3 H, m, ArH); δ_C(75.4 MHz; $CDCl_3$) −5.5 (2 C), 18.0, 25.7 (3 C), 28.2 (3 C), 37.6, 65.4, 72.7, 82.7, 126.0, 126.9, 128.1 (2 C), 129.9 (2 C), 134.7, 150.1, 153.4 and 169.5.

An alternative approach to **16** involved alkylation of **7** (0.6 g, 1.36 mmol) with benzyl bromide (2.3 cm^3, 13.6 mmol) according to the procedure described for **2** and gave the lactam **16** in 58% yield.

(±)-*N*-(*tert*-Butoxycarbonyl)-3-*O*-(*tert*-butyldimethylsilyl)-2-benzylserine 17. The title compound, prepared from the lactam **16** (220 mg, 0.52 mmol) by following the procedure described for the amino acid **12**, was obtained as a *colourless glassy solid* (85 mg, 40%) (Found: C, 61.3; H, 8.7; N, 3.2. $C_{21}H_{35}NO_5Si$ requires C, 61.6; H, 8.6; N, 3.4%); δ_H(300 MHz; $CDCl_3$) 0.08 (6 H, s, Me), 0.90 (9 H, s, Bu^t), 1.46 (9 H, s, Bu^t), 3.10 (1 H, 1/2 AB q, J 13.4, 1/2 CH_2Ph), 3.48 (1 H, 1/2 AB q, J 13.4, 1/2 CH_2Ph), 3.99 (1 H, 1/2 AB q, J 10.0, 1/2 CH_2O), 4.18 (1 H, 1/2 AB q, J 10.0, 1/2 CH_2O), 5.33 (1 H, s, NH), 7.15 (2 H, m, ArH) and 7.24 (3 H, m, ArH); δ_C(75.4 MHz; $CDCl_3$) −5.6 (2 C), 18.0, 25.6 (3 C), 28.2 (3 C), 36.6, 64.2, 65.5, 79.8, 126.8, 128.1 (2 C), 129.8 (2 C), 135.2, 154.5 and 175.6; m/z (CI, methane) 410 (M + H)$^+$.

(±)-Benzylserine 18. The title compound, prepared from the protected derivative **17** (85 mg, 0.21 mmol) by following the procedure described for **14**, was obtained as a *glass* (39 mg, 95%) HCl salt: (Found: C, 51.5; H, 6.2; N, 5.8. $C_{10}H_{14}ClNO_3$ requires C, 51.8; H, 6.1; N, 6.1%); δ_H(300 MHz; CD_3OD) 3.01 (1 H, 1/2 AB q, J 14.3, 1/2 CH_2Ph), 3.21 (1 H, 1/2 AB q, J 14.3, 1/2 CH_2Ph), 3.71 (1 H, 1/2 AB q, J 11.7, 1/2 CH_2O), 3.98 (1 H, 1/2 AB q, J 11.7, 1/2 CH_2O), 7.19 (2 H, m, ArH) and 7.26 (3 H, m, ArH); δ_C(75.4 MHz; CD_3OD) 39.2, 64.9, 66.8, 129.1, 129.9 (2 C), 131.2 (2 C), 134.0 and 171.6; m/z (CI, methane) 196 (M + H)$^+$.

(±)-*threo*-4-(*tert*-Butoxycarbonylamino)-5-(*tert*-butyldimethylsiloxy)hex-2-enoic acid 1,4-lactam 19. The title compound, prepared from the enol ether **5** (0.9 g, 3.1 mmol) and acetaldehyde (0.2 cm^3, 3.5 mmol) by following the procedure

described for **16**, was obtained as a *white glassy solid* (565 mg, 51%) (Found: C, 60.9; H, 9.6; N, 3.6. $C_{18}H_{33}NO_4Si$ requires C, 60.8; H, 9.4; N, 3.9%); δ_H(300 MHz; $CDCl_3$) 0.08 (6 H, s, Me), 0.90 (9 H, s, Bu^t), 1.22 (3 H, d, *J* 6.5, Me), 1.47 (3 H, s, Me), 1.54 (9 H, s, Bu^t), 4.59 (1 H, q, *J* 6.5, 5-H), 6.04 (1 H, d, *J* 6.1, 2-H) and 7.04 (1 H, d, *J* 6.1, 3-H); δ_C(75.4 MHz; $CDCl_3$) −4.5 (2 C), 17.6, 19.9, 25.5 (3 C), 28.1 (3 C), 29.7, 69.1, 76.2, 82.4, 126.0, 152.4, 154.6 and 169.5.

(±)-*N*-(*tert*-Butoxycarbonyl)-3-*O*-(*tert*-butyldimethylsilyl)-2-methylthreonine 20. The title compound, prepared from compound **19** (565 mg, 1.59 mmol) by following the procedure described for the amino acid **12**, was obtained as a *glassy solid* (200 mg, 36%) (Found: C, 55.0; H, 9.5; N, 4.2. $C_{16}H_{33}NO_5Si$ requires C, 55.3; H, 9.6; N, 4.0%); δ_H(300 MHz; $CDCl_3$) 0.07 (6 H, s, Me), 0.91 (9 H, s, Bu^t), 1.24 (3 H, d, *J* 7.3, Me), 1.50 (3 H, s, Me), 1.56 (9 H, s, Bu^t) and 4.12 (1 H, q, *J* 7.3, 3-H); δ_C(75.4 MHz; $CDCl_3$) −4.5 (2 C), 18.0, 19.1, 22.5, 25.5 (3 C), 28.8 (3 C), 66.5, 72.3, 82.4, 150.5 and 175.2; *m*/*z* (CI, methane) 348 $(M + H)^+$.

(±)-α-Methylthreonine 21. The title compound, prepared from the protected derivative **20** (200 mg, 0.58 mmol) by following the procedure described for **14**, was obtained as a *white powder* (76 mg, quantitative), mp 208–215 °C [lit.,[5g] 211–213 °C (2*R*,3*S*-enantiomer); 214–219 °C (2*S*,3*R*-enantiomer)]; HCl salt: (Found: C, 35.3; H, 7.3; N, 8.0. $C_5H_{12}ClNO_3$ requires C, 35.4; H, 7.1; N, 8.3%); δ_H(300 MHz; D_2O) 1.22 (3 H, d, *J* 6.8, Me), 1.35 (3 H, s, Me), 4.15 (1 H, q, *J* 6.8, 3-H); *m*/*z* (CI, methane) 134 $(M + H)^+$. The ^1H NMR data agree with those reported by Ohfune for (2*R*,3*S*)-2-methylthreonine.[5g]

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