View Article Online / Journal Homepage / Table of Contents for this issue

1 PERKIN

Approaches to the synthesis of (2*R*,3*S*)-2-hydroxymethylpyrrolidin-3-ol (CYB-3) and its C(3) epimer: a cautionary tale

Alison N. Hulme * and Karen S. Curley

Department of Chemistry, The University of Edinburgh, Kings Buildings, West Mains Road, Edinburgh, UK EH9 3JJ

Received (in Cambridge, UK) 14th January 2002, Accepted 22nd February 2002
First published as an Advance Article on the web 26th March 2002

Published on 26 March 2002. Downloaded by University of Western Ontario on 28/10/2014 10:15:46.

The syntheses of (2*R*,3*S*)-2-*tert*-butyldiphenylsilyloxymethylpyrrolidin-3-ol (TBDPS-protected CYB-3) (**21**) and its C(3) epimer (**25**) have been achieved in 9 and 8 steps respectively from D-serine. However, chiral HPLC analysis of the key β-hydroxy ester intermediates in these syntheses (**17** and **18**) revealed that appreciable levels of racemisation had occurred in the aldol and Claisen condensation reactions used in this synthetic sequence.

Introduction

The hydroxypyrrolidine CYB-3 (**1**),[1] shares its biological source (a tree from *Castanospermum australe* sp.) with the more well known indolizidine alkaloid castanospermine (**2**) (Fig. 1).[2]

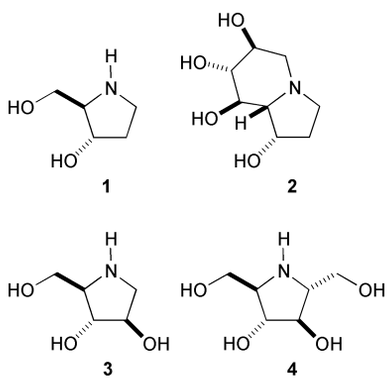


Fig. 1 Alkaloid glycosidase inhibitors.

Although CYB-3 exhibits only modest inhibitory activity against several insect[3] and mammalian[4] glycosidase targets when compared with other pyrrolidine alkaloids such as 1,4-dideoxy-1,4-imino-D-arabinitol (DAB-1) (**3**),[5] and (2*R*,3*R*,4*R*,5*R*)-2,5-bis(hydroxymethyl)-3,4-dihydroxypyrrolidine (DMDP) (**4**),[6] it has been proposed as both a chemical[7] and biosynthetic[8] precursor for a number of more active indolizidine alkaloids and has also been used in the synthesis of modified oligonucleotides.[9]

Several chemical syntheses of CYB-3 (**1**) have been reported recently which rely upon readily available chiral pool starting materials. In approaches utilising the amino acid serine (**5**), a number of different strategies have been used to achieve the required two-carbon homologation; the most common of these involving allylation and subsequent oxidative cleavage to remove the "extra" carbon.[10] However, two-carbon homologation has also been achieved through the use of vinyl Grignard addition[9] and Horner–Wadsworth–Emmons (HWE)/cyclocarbamation reactions,[7] as well as the tandem Michael/Henry reaction of a nitroethylene precursor.[11] Other popular chiral pool starting materials for the synthesis of CYB-3 include pyroglutamic acid† (**6**)[12] and sugars such as mannose (**7**)

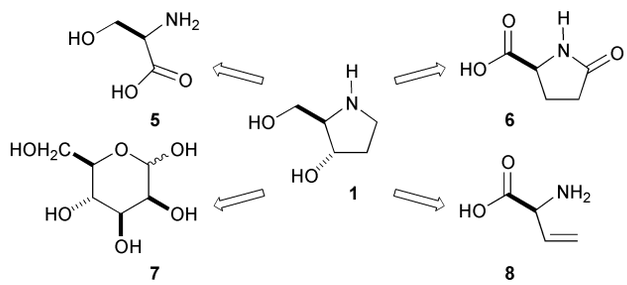


Fig. 2 Chiral pool precursors to CYB-3.

(Fig. 2).[13] One final approach from the chiral pool utilises the olefin metathesis of a derivative of vinyl glycine (**8**) as the key step.[14]

We have recently reported the syntheses of both the iminosugar DAB-1 (**3**),[15] and the antibiotic anisomycin (**9**),[16] utilising stereocontrolled glycolate aldol couplings to D-serine- and D-tyrosine-derived aldehydes **10** and **11** respectively to provide the acyclic backbone of each of these natural products in high yield (Fig. 3).

As part of a continued interest in the synthesis of bioactive iminosugars through the use of the aldol reaction, we were

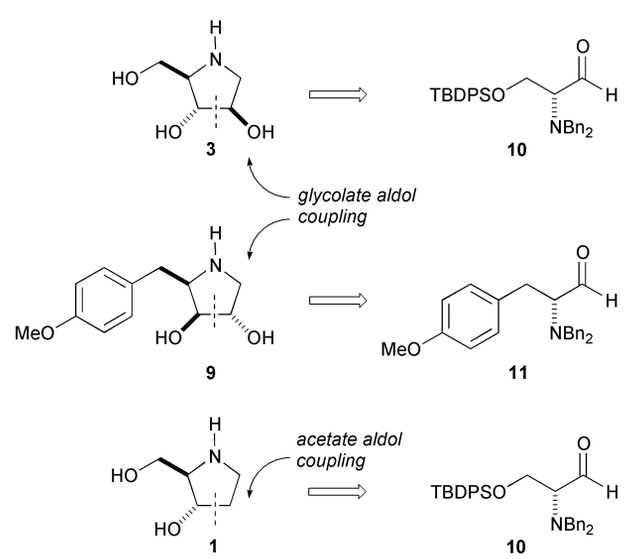


Fig. 3 An aldol based approach to the syntheses of the hydroxylated pyrrolidines DAB-1, anisomycin and CYB-3.

† Pyroglutamic acid is also known as 5-oxoproline.

DOI: 10.1039/b200415a

This journal is © The Royal Society of Chemistry 2002

View Article Online

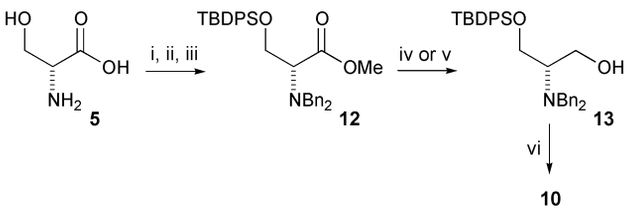
Published on 26 March 2002. Downloaded by University of Western Ontario on 28/10/2014 10:15:46.

attracted to the possibility of an acetate aldol approach to the synthesis of CYB-3 (**1**), combining the lithium enolate of methyl, or ethyl acetate with our readily accessible D-serine-derived aldehyde **10**. Previous reports of such acetate aldols have shown that high levels of substrate-derived stereocontrol might be achieved in the case of simple *N*,*N*-dibenzyl α-amino aldehydes,[17] and that this strategy might be successfully extended to the reaction of more sterically demanding aldehydes such as that derived from isoleucinal.[18]

Results and discussion

Synthesis of (2*R*,3*S*)-2-*tert*-butyldiphenylsilyloxymethyl-pyrrolidin-3-ol

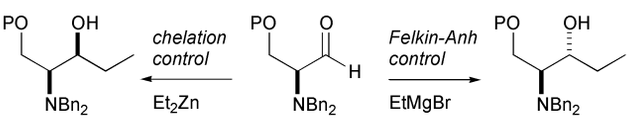
The synthesis of aldehyde **10** from D-serine (**5**) was carried out in five steps as described in our previous paper (Scheme 1).[15]



Scheme 1 *Reagents and conditions*: i. CH_3COCl, MeOH, reflux, 3 h (98%); ii. K_2CO_3, BnBr, CH_3CN, rt, 24 h (95%); iii. TBDPSCl, imidazole, DMF, rt, 18 h (100%); iv. DIBAL-H, $PhCH_3$, −78 °C, 30 min (93%); v. $LiBH_4$, Et_2O : MeOH (60 : 1), 0 °C ⟶ reflux, 4 h (95%); vi. $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h, Et_3N (100%).

However, on a gram scale the removal of copious quantities of aluminium salts from the DIBAL-H reduction of methyl ester **12** was found to be troublesome, and $LiBH_4$ reduction of the ester **12** to the corresponding alcohol **13** was preferred (95%). Using this modified protocol, aldehyde **10** could routinely be prepared in 88% overall yield from serine.

High levels of substrate based stereocontrol have been observed in the reactions of L-serine-derived *N*,*N*-dibenzyl α-amino aldehyde **14a** and its TBDMS-protected analogue **14b** with simple nucleophiles, by ourselves[19] and Andrés and Pedrosa.[20] Thus aldehydes **14a**,**b** have been shown to react with Grignard reagents to give the *anti* addition products **15a**,**b** with >95 : 5 selectivity due to Felkin–Anh control (Fig. 4),

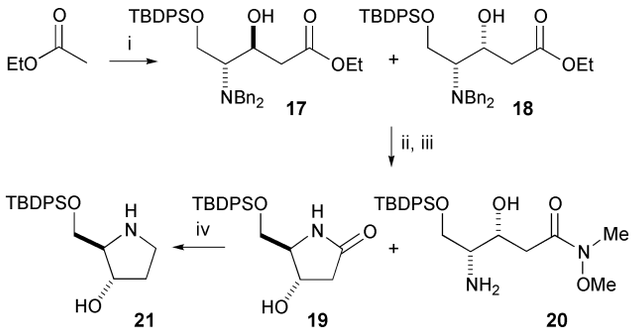


16a d.r. >99:1 **14a** P = TBDPS **15a** d.r. 95:5
16b d.r. >99:1 **14b** P = TBDMS **15b** d.r. 95:5

Fig. 4 Felkin–Anh and chelation control in the reaction of simple nucleophiles with *N*,*N*-dibenzyl α-amino aldehydes **14**.

whereas the reaction of dialkylzinc reagents has been shown to proceed with excellent selectivity for the *syn* addition products **16a**,**b**, presumably due to a chelation controlled mechanism.

With the knowledge that these simple nucleophilic addition reactions to the enantiomeric protected serine-derived aldehyde **14a** proceeded with excellent stereocontrol, and the precedent of high substrate-derived selectivity in previous reactions of methyl, or ethyl acetate aldol reactions with simple *N*,*N*-dibenzyl α-amino aldehydes,[17,18] we were confident in achieving high levels of stereocontrol when following the synthetic pathway towards CYB-3 **1** outlined in Scheme 2. However, when aldehyde **10** was condensed with the lithium enolate of ethyl acetate the aldol adducts **17** and **18** were generated in good



Scheme 2 *Reagents and conditions*: i. LiHMDS, THF, −78 °C, 20 min; **10**, THF, −78 °C ⟶ 0 °C, 3 h (85%); ii. (MeO)NHMe·HCl, Me_3Al, THF, 0 °C ⟶ 35 °C, 3 h (98%); iii. $Pd(OH)_2$/C cat., MeOH, H_2, rt, 12 h (81% **19**, 12% **20**); iv. BH_3·THF, THF, 0 °C ⟶ reflux, 24 h (85%).

yield (85%),‡ but disappointingly were obtained as a 6 : 1 inseparable mixture of diastereomers [as determined by integration of the C(2) signals in the crude proton NMR spectrum].§

To complete the synthesis of CYB-3 we chose to pursue a similar route to that used in the synthesis of DAB-1,[15] namely cyclisation to give the pyrrolidin-2-one followed by borane reduction to give the requisite protected pyrrolidine. To facilitate the complete removal of the *N*-benzyl protecting groups from the mixture of aldol adducts[15] they were first converted in excellent yield into the corresponding Weinreb amides. These amides were then treated under standard deprotection conditions [$Pd(OH)_2$/C, H_2] to yield a readily separable mixture of products in which the Weinreb amide resulting from desired aldol adduct **17** had undergone a spontaneous cyclisation to give pyrrolidinone **19** (81%), whilst the minor diastereomer was isolated as the acyclic amino amide **20** (12%). The pyrrolidinone **19** was found to be a crystalline solid, allowing its structure to be determined unequivocally by X-ray diffraction. This fortuitous separation allowed the subsequent borane reduction to be conducted on a single diastereomer, and conversion of pyrrolidinone **19** to the desired protected pyrrolidine **21** was achieved in high yield (85%).

Thus a 9 step synthesis of TBDPS-protected CYB-3 **21** has been achieved in 50% overall yield. This protected derivative is ideally suited towards further synthetic manipulation such as that followed by Herdewijn *et al.* in the synthesis of modified oligonucleotides.[9] Furthermore, **21** and its protected pyrrolidinone precursor **19**, offer the opportunity for the development of new selective glycomimetic-based glycosyltransferase inhibitors,[21] through selective glycosylation of the CYB-3 core. [There are for example, only a few reported syntheses of motifs related to the oligosaccharide sialyl Lewis X currently reported in the literature based on mono- or disaccharide derivatives of a pyrrolidinone,[22] or pyrrolidine core.[23]]

Synthesis of (2*R*,3*R*)-2-*tert*-butyldiphenylsilyloxymethyl-pyrrolidin-3-ol

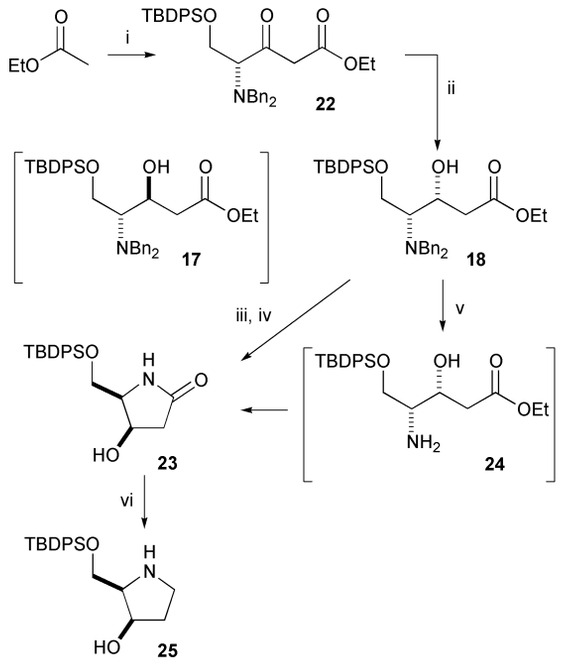
In tackling the synthesis of the C(3) epimer we felt that we should make use of the high substrate-derived selectivity that is normally observed in the Felkin–Anh controlled reduction of *N*,*N*-dibenzyl α-amino ketones.[17a] The *N*,*N*-dibenzyl α-amino ketone that was required for this strategy was obtained from the

‡ R_t *anti* diastereomers (aldol major) **17** and *ent*-**17**, 8.3 and 9.0 min; R_t *syn* diastereomers (Claisen major) **18** and *ent*-**18**, 9.1 and 10.8 min [4.6 × 250 mm Chiracel OD column, solvent (5% isopropyl alcohol (IPA) in hexane), flow rate 0.5 mL min^{-1}].

§ Unfortunately, all attempts to improve the diastereoselectivity of this acetate aldol reaction through the use of 'matched' chiral acetate boron enolates (from either the phenylalanine-derived acylated Evans oxazolidinone, or valine-derived acylated thiazolidinethione) were unsuccessful. These reactions resulted in lower yields of reaction products, with no significant improvement in the diastereoselectivity.

View Article Online

Published on 26 March 2002. Downloaded by University of Western Ontario on 28/10/2014 10:15:46.



Scheme 3 *Reagents and conditions:* i. LiHMDS, THF, −78 °C, 25 min; **12**, THF, −78 °C ⟶ 0 °C, 4 h (78%); ii. $NaCNBH_3$, AcOH, Et_2O : MeOH (8 : 3), 0 °C ⟶ rt, 7 h (81%); iii. (MeO)NHMe, Me_3Al, THF, 0 °C ⟶ 35 °C, 3 h (95%); iv. $Pd(OH)_2/C$, MeOH, H_2, rt, 12 h; SiO_2; MeOH, reflux, 24 h (72%); v. $Pd(OH)_2$, MeOH, H_2, rt, 12 h; SiO_2; MeOH, reflux, 24 h (78%); vi. BH_3·THF, THF, 0 °C ⟶ reflux, 24 h (86%).

Claisen condensation of methyl ester **12** (Scheme 1) with the lithium enolate of ethyl acetate to give **22** in good yield (78%, Scheme 3). Several different reagents, including sodium and lithium borohydride, were used for the selective reduction of the ketone functionality. Due to the hindered nature of this protected α-amino ketone this reaction was found to be extremely sluggish at 0 °C and heating to room temperature was required to drive the reaction to completion. This resulted in considerable concomitant reduction of the ester to give the corresponding diastereomeric diols. Thus although reasonable selectivity favouring the desired *syn* stereochemistry in **18** (typically 5 : 1 to 8 : 1) could be achieved, the yields of **18** and **17** were low. A solution was finally obtained with the use of sodium cyanoborohydride which, despite longer reaction times and the need for a greater excess of the reagent to drive the reaction to completion, resulted in a marked decrease in ester reduction. This allowed the synthesis of diastereomeric β-hydroxy esters **18** and **17** as a 10 : 1 mixture of diastereomers [as determined by integration of the C(2) signals in the crude ^{1}H NMR spectrum]. In this diastereomeric mixture, **18** was found to be amenable to chromatographic separation and could be isolated in 81% yield (along with 6% of **17**).

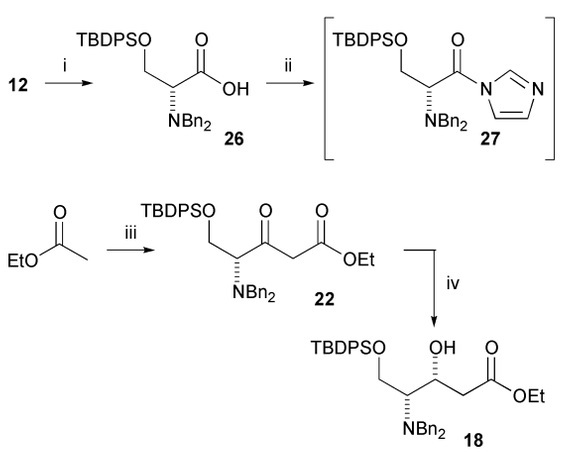
Two separate routes to the completion of the synthesis of the C(3) epimer of CYB-3 were pursued. In the first, the ester **18** was converted to the Weinreb amide as in the previous synthetic sequence [(MeO)NHMe·HCl, Me_3Al, 95%] and this was subjected to debenzylation [$Pd(OH)_2/C$, H_2] to give the amino amide **20**. This amide was filtered through a short pad of silica and then heated at reflux in methanol for 24 h, to give the pyrrolidinone **23** in 78% yield. The second, more direct route made use of the relatively lower reactivity towards cyclisation imparted on this stereoisomer by its conformation. (Thus debenzylation of the amino ester **18** might be expected to go to completion, without concomitant cyclisation to give a mixture of the desired product **23** and the corresponding benzyl protected pyrrolidinone.) When **18** was treated under standard conditions [$Pd(OH)_2/C$, H_2] for debenzylation, amino ester **24** was indeed isolated in excellent yield (100% crude material). Filtration through a short pad of silica and heating to reflux in methanol once again yielded pyrrolidinone **23** in high yield (78%). Borane reduction of pyrrolidinone **23** gave the desired protected pyrrolidine **25** in high yield (86%). Using the second (shorter) of these routes, a 7 step synthesis of the TBDPS-protected C(3) epimer of CYB-3 (**25**) from the amino acid serine, has been achieved in 39% overall yield.

The cautionary tale

There is literature precedent for the aldol reactions of simple lithium enolates with *N*,*N*-dibenzyl α-amino aldehydes, and little discussion of any loss of stereochemical integrity during the course of these reactions.[17,18] However, it is known that racemisation may occur in the Claisen condensation reaction of simple *N*,*N*-dibenzyl α-amino esters,[24] where the resultant enantiomeric excess may be reduced to as low as 78–90%. We were anxious to investigate whether, and if so the extent to which, racemisation had occurred in our current synthetic work.

We have previously shown that the synthetic sequence outlined in Scheme 1 allows the production of aldehyde **10** (and hence its precursors) with no appreciable racemisation (>98% ee by chiral HPLC) and indeed that high yields of a single diastereomer might be obtained in subsequent glycolate aldol couplings, suggesting no appreciable racemisation in the reaction of **10**.[15] In order to rapidly identify all four possible stereoisomers from the acetate aldol coupling, the synthesis of **17** and **18** was carried out using the route shown in Scheme 2 starting from a sample of aldehyde **10** prepared from racemic serine. The resultant β-hydroxy esters were separable by chiral HPLC using a standard analytical Chiracel OD column and a solvent mix of 5% IPA in hexane.‡ Comparison of this HPLC trace with those obtained from the aldol reaction of chiral non-*racemic* D-serine-derived aldehyde **10**, allowed us to draw the unhappy conclusion that our aldol adduct **17** was of only 90% ee. Worse still, the β-hydroxy ester **18** derived from the Claisen reaction of methyl ester **12** and subsequent cyanoborohydride reduction was shown to vary in enantiomeric excess from 0% to 70% in an extremely capricious manner.

In an effort to address the latter problem, alternative substrates for the Claisen condensation were sought. Saponification of the methyl ester to acid **26** and conversion to the imidazolide (acylimidazole) **27** is well-precedented in the literature for other α-amino esters.[24,25] However, in itself this presented problems in that methyl ester **12** was found to be relatively unreactive towards saponification under a range of standard conditions, including those recently published for sterically congested methyl esters of this type.[24] The most efficient conditions were found to be heating ester **12** to reflux in a THF–water solvent mixture in the presence of LiOH (Scheme 4). There was a delicate balance between the yield of



Scheme 4 *Reagents and conditions:* i. LiOH, THF : H_2O (4 : 1), reflux, 6 h (58%); ii. CDI, THF, rt, 2 h; iii. LiHMDS, THF, −78 °C, 20 min; **27**, THF, −78 °C ⟶ 0 °C, 2 h (91% from **26**); iv. $NaCNBH_3$, AcOH, Et_2O : MeOH (8 : 3), 0 °C ⟶ rt, 7 h (81%).

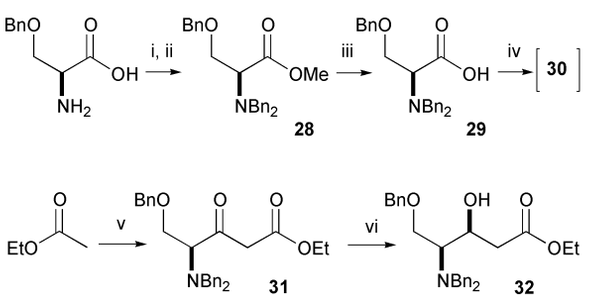
View Article Online

Published on 26 March 2002. Downloaded by University of Western Ontario on 28/10/2014 10:15:46.

acid **26** and the eventual enantiomeric excess of product **18**; longer reaction times (24 h) resulting in high yields of the acid (90%) but with considerable racemisation and concomitant loss of the TBDPS protecting group. Conversion to the imidazolide **27** using carbonyldiimidazole (CDI) was efficient, but in general **27** was not isolated, rather it was treated directly with the lithium enolate of ethyl acetate to give the amino ketone **22** in high yield (91% from acid **26**). Reduction under the previously optimised conditions ($NaCNBH_3$) allowed the synthesis and isolation of **18** and assessment of its enantiomeric purity by chiral HPLC. Using this route we were able to produce the β-hydroxy ester **18** with a reliable enantiomeric excess of 70%. This material was then converted through to the desired (2*R*,3*S*)-2-*tert*-butyldiphenylsilyloxymethylpyrrolidin-3-ol **25**, giving an 8 step synthesis of this protected hydroxypyrrolidine in 26% overall yield.

Since the enantiomeric excess observed in β-hydroxy ester **18** produced *via* the route shown in Scheme 4 was shown to be extremely dependent upon the conditions used for the saponification of methyl ester **12**, this suggested that in itself the use of the CDI-mediated Claisen condensation was not contributing greatly to the racemisation process (as compared to the direct condensation of methyl ester **12**). Indeed CDI-mediated coupling has been used in conjunction with a number of other *N*,*N*-dibenzylamino acids, without any apparent loss of stereochemical integrity.[24] This suggested that the problem perhaps arose from the extremely hindered nature of methyl ester **12**, due in part to the choice of the TBDPS protecting group. Thus a further solution to the problem of racemisation in the condensation route to the C(3) epimer of CYB-3 was sought through the synthesis of an *O*-benzyl protected acid derivative, which it was hoped would offer the same acid stability as its TBDPS counterpart, but with reduced steric bulk.

In order to test this hypothesis, the synthesis of methyl ester **28**, was undertaken in two steps from commercially available L-*O*-benzyl serine (Scheme 5). Saponification of ester **28** was



Scheme 5 *Reagents and conditions:* i. CH_3COCl, MeOH, reflux, 3 h (96%); ii. K_2CO_3, BnBr, CH_3CN, rt, 24 h (94%); iii. LiOH, THF : H_2O (4 : 1), reflux, 4 h (100%); iv. CDI, THF, rt, 2 h; v. LiHMDS, THF, −78 °C, 20 min; **30**, THF, −78 °C ⟶ 0 °C, 2.5 h (92% from **29**); vi. $NaCNBH_3$, AcOH, Et_2O : MeOH (2 : 1), 0 °C ⟶ rt, 8 h (90%).

found to be far more facile than its TBDPS counterpart **12**, and high yields of the desired acid **29** were achieved under a range of conditions including the use of LiOH, $Ba(OH)_2$, and KOH. The most efficient conditions were found to mimic those used for the TBDPS protected ester; heating a mixture of the ester **28** and LiOH to reflux in a THF–water solution (100%).¶ CDI-mediated coupling with the lithium enolate of ethyl acetate to give β-keto ester **31** was found to proceed extremely smoothly (92% from acid **29**). Finally, sodium cyanoborohydride reduction to amino alcohol **32** was used to assess the enantiomeric excess of the material that had been produced through comparison with an HPLC trace produced from a sample of racemic material.‖ However, in line with an observed $[\alpha]_D$ of 0° for both the acid **29** and α-amino ketone **31**, chiral HPLC confirmed that we once again had an enantiomeric excess of 0%.[26] Thus, despite this representing a higher-yielding approach to the desired protected CYB-3 C(3) epimer, this route was not pursued further.

Conclusions

We have shown that the aldol and imidazolide-mediated Claisen reactions of the lithium enolate of ethyl acetate with aldehyde **10** and acid **26** provide extremely attractive routes to the synthesis of silyl-protected CYB-3 and its C(3) epimer, in terms of both the number of steps and overall efficiency of the process. However, chiral HPLC analysis has revealed that for our TBDPS protected serine-derived system this efficiency is achieved at a price. Thus aldol adduct **17** is isolated in only 90% ee and Claisen–reduction product **18** is isolated in a modest 70% ee.

Our studies have highlighted in particular, problems with the synthesis of certain *O*-protected serine-derived *N*,*N*-dibenzyl α-amino acids required for use in this Claisen based approach to the C(3) epimer of CYB-3. However, a recent report of the synthesis of the *tert*-butyldimethylsilyl protected analogue of acid **26**, *via* deprotection of the corresponding allyl ester suggests that alternative routes to the desired acid might be possible.[27] Preliminary studies in our laboratories with other *N*,*N*-dibenzyl protected α-amino acids indicate that problems of racemisation using this route appear to be confined to the serine derivatives. Hence, we are currently undertaking studies to investigate the application of this approach to the synthesis of other pyrrolidine glycomimetics.

Experimental

General

All reactions involving air or water sensitive reagents were carried out under an atmosphere of argon using flame or oven-dried glassware. Unless otherwise noted, starting materials and reagents were obtained from commercial suppliers and were used without further purification. THF was distilled from Na–benzophenone ketyl immediately prior to use. Toluene, CH_2Cl_2, Et_3N, and DMF were distilled from calcium hydride. Anhydrous methanol and acetonitrile were used as supplied by Aldrich. Unless otherwise indicated, organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure using a rotary evaporator. Purification by flash column chromatography was carried out using Merck Kieselgel 60 silica gel as the stationary phase. Chiral HPLC was performed using a Waters instrument equipped with a UV detector and a Chiracel OD column (internal diameter 4.6 mm, length 250 mm). All solvents for use in HPLC analysis were vacuum filtered and degassed prior to use, and a standard flow rate of 0.5 mL min^{-1} was used. IR spectra were measured as thin films on NaCl plates, unless otherwise stated. Melting points were determined on a Gallenkamp Electrothermal Melting Point apparatus and are uncorrected. Optical rotations were measured (10^{-1} deg cm^2 g^{-1}) on a AA-1000 polarimeter with a path length of 1.0 dm, at the sodium D line, at room temperature. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 200, a Bruker AC250 or a Bruker AM360 spectrometer. Coupling constants *J* are reported in Hz. Elemental analysis was carried on a Perkin Elmer 2400 CHN Elemental Analyser. Fast atom bombardment (FAB) mass

¶ Prolonged exposure to these conditions (24 h) at room temperature was found to result in no conversion of the ester **28** to acid **29**.

‖ R_t *syn* diastereomers **32** and *ent*-**32**, 18.3 and 23.1 min [4.6 × 250 mm Chiracel OD column, solvent (5% IPA in hexane), flow rate 0.5 mL min^{-1}].

View Article Online

Published on 26 March 2002. Downloaded by University of Western Ontario on 28/10/2014 10:15:46.

spectra were obtained using a Kratos MS50TC mass spectrometer at The University of Edinburgh.

Synthesis of TBDPS-protected CYB-3

(2*S*)-3-*tert*-Butyldiphenylsilyloxy-2-(*N*,*N*-dibenzylamino)-propan-1-ol 13. To a solution of ester **12** (4.20 g, 7.82 mmol),[15] in anhydrous ether (60 cm^3) at 0 °C was added lithium borohydride (0.99 g, 49.9 mmol) followed by anhydrous methanol (1 cm^3). The mixture was stirred at 0 °C until effervescence ceased and then heated to reflux and held at reflux for 4 hours. Saturated aqueous NH_4Cl (140 cm^3) was added cautiously and the aqueous phase was extracted with DCM (3 × 100 cm^3). The combined organic phases were washed with brine (200 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane : EtOAc (5 : 1)] to give alcohol **13** (3.80 g, 95%) as an oil. R_f [hexane : EtOAc (4 : 1)] 0.55; all spectroscopic data were in good agreement with those reported previously.[15]

Ethyl (3*S*,4*R*)-5-*tert*-butyldiphenylsilyloxy-4-(*N*,*N*-dibenzylamino)-3-hydroxypentanoate 17. To a solution of LiHMDS (8.84 cm^3, 1.06 M in THF, 9.37 mmol) at −78 °C was added ethyl acetate (0.871 cm^3, 8.84 mmol). The solution was stirred at −78 °C for 20 minutes. A solution of the aldehyde **10** (1.49 g, 2.94 mmol) in THF (6 cm^3) was added dropwise *via* cannula. The reaction mixture was stirred at −78 °C for 30 minutes then allowed to warm to 0 °C over a period of 2 hours, then stirred at 0 °C for 20 minutes. Saturated aqueous NH_4Cl (50 cm^3) was added and the aqueous phase extracted with DCM (3 × 60 cm^3). The combined organic phases were washed with brine (60 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane : Et_2O (5 : 1)] to give the title compound (1.48 g, 85%) as a 6 : 1 mixture of diastereomers. ν_{max} (neat)/cm^{-1} 3469, 2930, 1736, 1720, 1427; *m*/*z* (FAB) 596 ([M + H]$^+$, 14%), 478 (13), 268 (18), 135 (26), 91 (100); HRMS (FAB) $C_{37}H_{46}NO_4Si$ [*M* + H]$^+$ requires 596.3196, found 596.3192.

*Spectroscopic data for major diastereomer **17**.* R_f [hexane : Et_2O (1 : 1)] 0.40; δ_H (250 MHz, $CDCl_3$) 7.76–7.19 (20H, m, Ar*H*), 4.39–4.32 (1H, m, C(3)*H*OH), 4.25 (2H, q, *J* 7.2, OCH_2CH$_3$), 4.23–4.17 (1H, m, C(5)H_AH$_B$OTBDPS), 4.07 (1H, dd, *J* 10.6, 5.3, C(5)H$_A$$H_B$OTBDPS), 3.89 (2H, d, *J* 13.6, NCH_XH$_Y$Ph × 2), 3.58 (2H, d, *J* 13.6, NCH$_X$$H_Y$Ph × 2), 3.45 (1H, br s, O*H*), 2.98 (1H, dd, *J* 16.3, 2.7, C(2)H_CH$_D$), 2.78 (1H, br ddd, *J* 10.6, 8.7, 5.3, C(4)*H*), 2.31 (1H, dd, *J* 16.3, 8.7, C(2)H$_C$$H_D$), 1.28 (3H, t, *J* 7.2, OCH$_2$CH_3), 1.09 (9H, s, ^{t}*Bu*); δ_C (62.9 MHz) 173.0 (C), 139.6 (C), 135.6 (CH), 132.8 (C), 132.7 (C), 128.9 (CH), 128.7 (CH), 128.2 (CH), 127.7 (CH), 126.9 (CH), 68.1 (CH), 61.2 (CH), 60.9 (CH$_2$), 60.4 (CH$_2$), 55.1 (CH$_2$), 50.0 (CH$_2$), 39.5 (CH$_2$), 26.8 (CH$_3$), 19.0 (C), 14.1 (CH$_3$).

*Spectroscopic data for minor diastereomer **18**.* R_f [hexane : Et_2O (1 : 1)] 0.38; δ_H (250 MHz, $CDCl_3$) data were in good agreement with those reported below, diagnostic signal at 2.45 (1H, dd, *J* 15.2, 3.0, C(2)H_CH$_D$).

(4*S*,5*R*)-5-*tert*-Butyldiphenylsilyloxymethyl-4-hydroxypyrrolidin-2-one 19. *Preparation of the Weinreb amides.* To a slurry of *N*,*O*-dimethylhydroxylamine·hydrochloride (494 mg, 5.04 mmol) in THF (3 cm^3) at 0 °C was added trimethylaluminium (2.52 cm^3, 2.0 M in toluene, 5.04 mmol). The solution was stirred at 0 °C for 5 minutes then allowed to warm to room temperature over *ca.* 15 minutes, after which time a clear solution remained. The (6 : 1) mixture of aldol adducts **17** and **18** (500 mg, 0.839 mmol) in THF (4 cm^3) was added dropwise *via* cannula. The reaction mixture was warmed to 35 °C and stirred for 3 hours. The reaction mixture was cooled and then cannulated rapidly into a mixture of DCM (30 cm^3) and saturated aqueous potassium sodium tartrate (30 cm^3) and stirred vigorously for 5 hours whereupon two distinct phases were apparent. The aqueous phase was extracted with DCM (3 × 30 cm^3). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane : EtOAc (4 : 1)] to give a 6 : 1 mixture of diastereomeric amides (506 mg, 98%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3457, 3069, 2937, 2856, 1643, 1427; *m*/*z* (FAB) 611 ([M + H]$^+$, 27%), 478 (36), 210 (11) 197 (20) 135 (41), 91 (100); HRMS (FAB) $C_{37}H_{47}N_2O_4Si$ [*M* + H]$^+$ requires 611.3305, found 611.3290.

*Spectroscopic data for major diastereomer (from **17**): (3S,4R)-5-tert-butyldiphenylsilyloxy-4-(N,N-dibenzylamino)-3-hydroxy-N-methoxy-N-methylpentanamide.* R_f [hexane : EtOAc (4 : 1)] 0.35; δ_H (360 MHz, $CDCl_3$) 7.83–7.24 (20H, m, Ar*H*), 4.39–4.32 (1H, m, C(3)*H*OH), 4.27 (1H, dd, *J* 10.9, 4.0, C(5)H_AH$_B$OTBDPS), 4.14 (1H, dd, *J* 10.9, 6.4, C(5)H$_A$$H_B$OTBDPS), 3.99 (2H, d, *J* 13.7, NCH_XH$_Y$Ph × 2), 3.80 (2H, d, *J* 13.7, NCH$_X$$H_Y$Ph × 2), 3.66 (3H, s, O*Me*), 3.21 (3H, s, *Me*), 2.89–2.82 (1H, m, C(4)*H*), 2.80–2.73 (1H, br m, C(2)$H_A$$H_B$), 2.32–2.25 (1H, br m, C(2)H$_A$$H_B$), 1.18 (9H, s, ^{t}*Bu*); δ_C (62.9 MHz) 174.8 (C), 140.7 (C), 136.3 (CH), 136.2 (CH), 133.8 (C), 133.6 (C), 130.2 (CH), 129.6 (CH), 129.4 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 127.3 (CH), 67.6 (CH), 66.6 (CH$_3$), 62.2 (CH), 61.7 (CH$_2$), 55.7 (CH$_2$), 37.1 (CH$_2$), 32.3 (CH$_3$), 27.4 (CH$_3$), 19.6 (C).

*Spectroscopic data for minor diastereomer (from **18**).* R_f [hexane : EtOAc (4 : 1)] 0.34; δ_H (360 MHz, $CDCl_3$) data were in good agreement with those reported below, diagnostic signals at 3.60 (3H, s, O*Me*), 2.69–2.58 (1H, br m, C(2)H_CH$_D$).

Reaction of the Weinreb amides. To a solution of the 6 : 1 mixture of Weinreb amides (420 mg, 0.689 mmol) in methanol was added 20% $Pd(OH)_2$/C (420 mg), the flask was flushed with argon before being stirred under an atmosphere of hydrogen for 12 hours. The reaction mixture was filtered through a layer of Celite and concentrated under reduced pressure. The residue was chromatographed on silica gel [DCM : MeOH (50 : 1)] to give pyrrolidinone **19** (206 mg, 81%) as a white solid and amino amide **20** (35 mg, 12%) as a colourless oil.

R_f [DCM : MeOH (10 : 1)] 0.32; mp 117–118 °C (hexane : EtOAc); $[\alpha]_D$ +17.2 (*c* 0.36, $CHCl_3$) (90% ee); ν_{max} (solution cell)/cm^{-1} 3200, 2910, 1678, 1426; δ_H (250 MHz, $CDCl_3$) 7.64–7.59 (4H, m, Ar*H*), 7.43–7.32 (6H, m, Ar*H*), 6.40 (1H, s, N*H*), 4.30–4.28 (1H, m, C(4)*H*OH), 3.63–3.60 (4H, m, C(3)H_2 + C(5)*H* + O*H*), 2.74 (1H, dd, *J* 17.2, 6.8, CH_AH$_B$OTBDPS), 2.30 (1H, dd, *J* 17.2, 2.9, CH$_A$$H_B$OTBDPS), 1.00 (9H, s, ^{t}*Bu*); δ_C (62.9 MHz) 176.4 (C), 135.4 (CH), 135.3 (CH), 132.6 (C), 132.4 (C), 129.8 (CH), 127.7 (CH), 69.5 (CH), 64.7 (CH$_2$), 64.5 (CH), 40.0 (CH$_2$), 26.6 (CH$_3$), 18.9 (C); *m*/*z* (FAB) 370 ([M + H]$^+$, 68%), 312 (15), 292 (53), 234 (27), 214 (61), 135 (100); HRMS (FAB) $C_{21}H_{28}NO_3Si$ [*M* + H]$^+$ requires 370.1838, found 370.1830.

*(3R,4R)-4-Amino-5-tert-butyldiphenylsilyloxy-3-hydroxy-N-methyl-N-methoxypentanamide **20**.* R_f [DCM : MeOH (10 : 1)] 0.12; δ_H (250 MHz, $CDCl_3$) 8.14–8.12 (2H, br s, NH_2), 7.60–7.32 (10H, m, Ar*H*), 4.25–4.20 (1H, br m, C(3)*H*OH), 4.01–3.85 (2H, m, C(5)H_2OTBDPS), 3.50 (3H, s, O*Me*), 2.97 (3H, s, *Me*), 2.90–2.82 (2H, br m, C(2)H_CH$_D$ + C(4)*H*), 2.39–2.30 (1H, br m, C(2)H$_C$$H_D$), 1.08 (9H, s, ^{t}*Bu*).

(2*R*,3*S*)-2-*tert*-Butyldiphenylsilyloxymethylpyrrolidin-3-ol 21. To a solution of the pyrrolidinone **19** (120 mg, 0.332 mmol) in THF (5 cm^3) at 0 °C was added BH_3·THF complex (4.95 cm^3, 1.0 M in THF, 4.95 mmol). The solution was stirred at 0 °C until effervescence ceased and then stirred at reflux for 24 hours. Methanol was added cautiously to the cooled (0 °C) reaction mixture. The resulting mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel [DCM : MeOH (50 : 1)] to give the pyrrolidine **21** (100 mg, 85%) as a white solid. R_f [DCM : MeOH (10 : 1)] 0.27; mp 105–106 °C; $[\alpha]_D$ +33.3 (*c* 0.09, $CHCl_3$) (90% ee); δ_H (250 MHz, $CDCl_3$)

View Article Online

Published on 26 March 2002. Downloaded by University of Western Ontario on 28/10/2014 10:15:46.

7.65–7.61 (4H, m, Ar*H*), 7.50–7.37 (6H, m, Ar*H*), 4.35 (1H, ddd, *J* 11.0, 7.4, 4.3, C(3)*H*OH), 4.19 (1H, dd, *J* 11.1, 3.0, CH_AH$_B$OTBDPS), 3.80 (1H, dd, *J* 11.1, 2.4, CH$_A$$H_B$OTBDPS), 3.37 (1H, ddd, *J* 11.7, 8.0, 7.4, C(5)H_EH$_F$), 3.21 (1H, ddd, *J* 11.7, 9.4, 4.3, C(5)H$_E$$H_F$), 2.94 (1H, ddd, *J* 11.0, 3.0, 2.4 C(2)*H*), 2.14 (1H, ddt, *J* 16.2, 9.4, 7.4, C(4)H_CH$_D$), 1.99 (1H, ddt, *J* 16.2, 8.0, 4.3, C(4)H$_C$$H_D$), 1.74 (1H, br s, O*H*), 1.06 (9H, s, ^{t}*Bu*); δ_C (62.9 MHz) 135.4 (CH), 132.2 (CH), 131.8 (C), 130.1 (CH), 127.9 (CH), 74.0 (CH), 73.1 (CH), 59.5 (CH_2), 53.0 (CH_2), 34.1 (CH_2), 26.8 (CH_3), 19.2 (C); *m*/*z* (FAB) 356 ([M + H]$^+$, 65%), 278 (26), 197 (53), 183 (22), 135 (100); HRMS (FAB) $C_{21}H_{30}NO_2Si$ [*M* + H]$^+$ requires 356.2046, found 356.2046.

Synthesis of the C(3) epimer of TBDPS-protected CYB-3

(2*R*)-3-*tert*-butyldiphenylsilyloxy-2-(*N*,*N*-dibenzylamino)-propanoic acid 26. To a solution of methyl ester **12** (500 mg, 0.931 mmol) in THF (15 cm^3) was added dropwise a slurry of LiOH·H$_2$O (195 mg, 4.65 mmol) in H$_2$O (3.75 cm^3). The solution was heated to reflux and held at reflux for 6 hours. The solution was cooled to room temperature and H$_2$O (15 cm^3) was added. The aqueous phase was extracted with EtOAc (2 × 25 cm^3) then the mixture was acidified to pH 3 with 1 M HCl and the aqueous phase was extracted with Et$_2$O (3 × 20 cm^3). The combined organic phases were dried (MgSO$_4$) and concentrated under reduced pressure to give acid **26** (280 mg, 58%) as a tacky solid. R_f [hexane : EtOAc (4 : 1)] 0.20; $[\alpha]_D$ −15.45 (*c* 0.22, CHCl$_3$) (70% ee); ν_{max} (neat)/cm^{-1} 3200, 3069, 2930, 2856, 1709, 1428; δ_H (250 MHz, CDCl$_3$) 7.79–7.29 (20H, m, Ar*H*), 4.21–4.12 (2H, m, CH_2OTBDPS), 4.09 (2H, d, *J* 13.5, NCH_XH$_Y$Ph × 2), 4.03 (2H, d, *J* 13.5, NCH$_X$$H_Y$Ph × 2), 3.09 (1H, dd, *J* 8.5, 5.1, C(2)*H*), 1.16 (9H, s, ^{t}*Bu*); δ_C (62.9 MHz) 172.3 (C), 137.2 (C), 136.1 (CH), 135.9 (CH), 133.0 (C), 132.9 (C), 130.5 (CH), 129.5 (CH), 129.3 (CH), 128.5 (CH), 128.4 (CH), 128.1 (CH), 63.5 (CH), 62.3 (CH_2), 55.6 (CH_2), 27.4 (CH_3), 19.6 (C); *m*/*z* (FAB) 524 ([M + H]$^+$, 56%), 154 (44), 136 (37), 107 (16), 91 (100); HRMS (FAB) $C_{33}H_{38}NO_3Si$ [*M* + H]$^+$ requires 524.2621, found 524.2622.

Ethyl (4*R*)-5-*tert*-butyldiphenylsilyloxy-4-(*N*,*N*-dibenzylamino)-3-oxopentanoate 22. *From methyl ester **12**.* To a solution of LiHMDS (2.79 cm^3, 1.06 M in THF, 2.79 mmol) at −78 °C was added ethyl acetate (0.270 cm^3, 1.21 mmol) and the solution stirred at −78 °C for 25 min. Methyl ester **12** (300 mg, 0.560 mmol) in THF (4 cm^3) was added *via* cannula and the resultant solution stirred at −78 °C for 3 hours then warmed to 0 °C and stirred at 0 °C for 1 hour. The reaction was quenched by the addition of saturated aqueous NH$_4$Cl (10 cm^3) and the aqueous phase was extracted with DCM (3 × 10 cm^3). The combined organic phases were washed with brine (20 cm^3), dried (MgSO$_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane : Et$_2$O (10 : 1)] to give the β-keto ester **22** as a pale yellow oil (260 mg, 78%). R_f [hexane : EtOAc (4 : 1)] 0.62; ν_{max} (neat)/cm^{-1} 3069, 2930, 2856, 1745, 1716, 1427; δ_H (250 MHz, CDCl$_3$) 7.80–7.21 (20H, m, Ar*H*), 4.18 (2H, q, *J* 7.2, OCH_2CH$_3$), 4.17–4.09 (2H, m, CH_2OTBDPS), 3.92 (2H, d, *J* 13.6, NCH_XH$_Y$Ph × 2), 3.81 (2H, d, *J* 13.6 NCH$_X$$H_Y$Ph × 2), 3.76–3.72 (1H, m, C(4)*H*), 3.69 (1H, d, *J* 16.0, C(2)H_CH$_D$), 3.58 (1H, d, *J* 16.0, C(2)H$_C$$H_D$), 1.27 (3H, t, *J* 7.2, OCH$_2$CH_3), 1.14 (9H, s, ^{t}*Bu*); δ_C (62.9 MHz) 203.3 (C), 167.8 (C), 139.6 (C), 136.1 (CH), 136.0 (CH), 135.7 (C), 135.2 (C), 130.3 (CH), 129.4 (CH), 128.9 (CH), 128.7 (CH), 128.2 (CH), 128.1 (CH), 127.2 (CH), 67.6 (CH), 61.6 (CH_2), 60.7 (CH_2), 55.6 (CH_2), 47.5 (CH_2), 27.3 (CH_3), 19.6 (C), 14.5 (CH_3); *m*/*z* (FAB) 594 ([M + H]$^+$, 12%), 478 (204), 199 (12), 181 (7), 135 (33), 91 (100); HRMS (FAB) $C_{37}H_{44}NO_4Si$ [*M* + H]$^+$, requires 594.3040, found 594.3039

*From acid **26**.* To a solution of acid **26** (500 mg, 0.958 mmol) in THF (10 cm^3) was added 1,1'-carbonyldiimidazole (542 mg, 3.35 mmol). The solution was stirred at room temperature for 2 hours to generate imidazolide **27**. Meanwhile to a solution of LiHMDS (2.88 cm^3, 1.0 M in THF, 2.88 mmol) at −78 °C was added ethyl acetate (0.280 cm^3, 2.88 mmol) and the resultant solution was stirred for 20 min at −78 °C. The solution of imidazolide **27** in THF was added *via* cannula. The reaction mixture was stirred at −78 °C for 20 min and allowed to warm to 0 °C over 30 min and stirred for a further 1 hour at 0 °C. The reaction was quenched by the addition of saturated aqueous NH$_4$Cl (15 cm^3) and the aqueous phase was extracted with DCM (3 × 15 cm^3). The combined organic phases were washed with brine (30 cm^3), dried (MgSO$_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane : EtOAc (10 : 1)] to give the title compound **22** as a pale yellow oil (510 mg, 90%). R_f [hexane : EtOAc (4 : 1)] 0.62; $[\alpha]_D$ +33.6 (*c* 0.27, CHCl$_3$) (70% ee); all other spectroscopic data were identical to those obtained from the Claisen reaction of methyl ester **12**.

Ethyl (3*R*,4*R*)-5-*tert*-butyldiphenylsilyloxy-4-(*N*,*N*-dibenzylamino)-3-hydroxypentanoate 18. To a solution of β-keto ester **22** (360 mg, 0.621 mmol) in Et$_2$O (8 cm^3) and MeOH (3 cm^3) was added acetic acid (*ca.* 1 cm^3) until the solution was pH 4. The solution was cooled to 0 °C and sodium cyanoborohydride (385 mg, 6.22 mmol) was added. Once effervescence had ceased the resulting solution was stirred at room temperature for 7 hours. The reaction was quenched by the addition of a saturated solution of NH$_4$Cl (30 cm^3) and the aqueous phase was extracted with DCM (3 × 30 cm^3). The combined organic phases were washed with brine (40 cm^3), dried (MgSO$_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane : Et$_2$O (7 : 1)] to give the amino alcohol **18** (290 mg, 81%) as a colourless oil and amino alcohol **17** (21 mg, 6%) as a colourless oil.

*Spectroscopic data for major diastereomer **18**.* R_f [hexane : Et$_2$O (1 : 1)] 0.38; $[\alpha]_D$ −18.75 (*c* 1.6, CHCl$_3$) (70% ee); ν_{max} (neat)/cm^{-1} 3456, 3070, 2931, 2858, 1732, 1428; δ_H (250 MHz, CDCl$_3$) 7.76–7.24 (20H, m, Ar*H*), 4.24–4.20 (1H, m, C(3)*H*OH), 4.19 (2H, q, *J* 7.1, OCH_2CH$_3$), 4.18–4.06 (2H, m, CH_2OTBDPS), 4.05 (2H, d, *J* 13.3, NCH_XH$_Y$Ph × 2), 3.60 (2H, d, *J* 13.3, NCH$_X$$H_Y$Ph × 2), 2.77–2.72 (1H, m, C(4)*H*), 2.45 (1H, dd, *J* 15.2, 3.0, C(2)H_CH$_D$), 2.30 (1H, dd, *J* 15.2, 9.0, C(2)H$_C$$H_D$), 1.28 (3H, t, *J* 7.1, OCH$_2$CH_3), 1.15 (9H, s, ^{t}*Bu*); δ_C (62.9 MHz) 172.4 (C), 139.5 (C), 136.2 (CH), 136.1 (CH), 133.3 (C), 133.2 (C), 130.5 (CH), 130.4 (CH), 129.5 (CH), 128.9 (CH), 128.3 (CH), 127.7 (CH), 65.8 (CH), 63.4 (CH), 60.9 (CH_2), 60.6 (CH_2), 54.9 (CH_2), 40.1 (CH_2), 27.4 (CH_3), 19.6 (C), 14.6 (CH_3); *m*/*z* (FAB) 596 ([M + H]$^+$, 40%), 478 (51), 326 (12), 197 (12), 135 (26), 91 (100); HRMS (FAB) $C_{37}H_{46}NO_4Si$ [*M* + H]$^+$ requires 596.3196, found 596.3197.

*Spectroscopic data for minor diastereomer **17**.* R_f [hexane : Et$_2$O (1 : 1)] 0.40; spectroscopic data were in good agreement with those reported above.

(4*R*,5*R*)-5-*tert*-Butyldiphenylsilyloxymethyl-4-hydroxypyrrolidin-2-one 23. *Via the Weinreb amide.* To a slurry of *N*,*O*-dimethylhydroxylamine·hydrochloride (371 mg, 3.82 mmol) in THF (4 cm^3) at 0 °C was added trimethylaluminium (3.82 cm^3, 2.0 M in toluene, 7.64 mmol). The solution was stirred at 0 °C for 5 minutes then allowed to warm to room temperature over *ca.* 15 minutes, after which time a clear solution remained. Ester **18** (380 mg, 0.637 mmol) in THF (4 cm^3) was added dropwise *via* cannula. The mixture was warmed to 35 °C and stirred for 3 hours. The reaction mixture was cooled and then rapidly transferred by cannula into a mixture of DCM (30 cm^3) and saturated aqueous potassium sodium tartrate (30 cm^3) and stirred vigorously for 5 hours whereupon two distinct phases were apparent. The aqueous phase was extracted with DCM (3 × 30 cm^3).The combined organic phases were dried (MgSO$_4$) and concentrated under reduced pressure. The residue was

View Article Online

Published on 26 March 2002. Downloaded by University of Western Ontario on 28/10/2014 10:15:46.

chromatographed on silica gel [hexane : EtOAc (4 : 1) to give the Weinreb amide (370 mg, 95%) as a colourless oil.

(3R,4R)-5-tert-Butyldiphenylsilyloxy-4-(N,N-dibenzylamino)-3-hydroxy-N-methoxy-N-methylpentanamide. R_f [hexane : EtOAc (4 : 1)] 0.34; $[\alpha]_D$ −4.74 (*c* 0.45, $CHCl_3$) (70% ee); ν_{max} (neat)/cm^{-1} 3460, 3075, 2925, 2826, 1644, 1428; δ_H (360 MHz, $CDCl_3$) 7.82–7.24 (20H, m, Ar*H*), 4.28–4.20 (1H, m, C(3)*H*OH), 4.10 (1H, dd, *J* 10.9, 8.0, C(5)H_AH_BOTBDPS), 4.04 (2H, d, *J* 13.4, NCH_XH_YPh × 2), 4.00 (1H, dd, *J* 10.9, 5.4, C(5)H_AH_BOTBDPS), 3.91 (2H, d, *J* 13.4, NCH_XH_YPh × 2), 3.60 (3H, s, O*Me*), 3.20 (3H, s, *Me*), 2.80–2.73 (1H, m, C(4)*H*), 2.69–2.58 (1H, br m, C(2)H_CH_D), 2.30–2.19 (1H, br m, C(2)H_CH_D), 1.12 (9H, s, ^tBu); δ_C (90.6 MHz) 173.6 (C), 140.2 (C), 136.2 (CH), 136.1 (CH), 133.6 (C), 133.5 (C), 130.4 (CH), 130.3 (CH), 129.6 (CH), 128.7 (CH), 128.3 (CH), 127.4 (CH), 66.7 (CH), 63.6 (CH_3), 61.5 (CH), 61.4 (CH_2), 55.4 (CH_2), 37.2 (CH_2), 32.4 (CH_3), 27.4 (CH_3), 19.6 (C); *m*/*z* (FAB) 416 ([M + H]$^+$, 72%), 478 (81), 341 (17), 197 (43), 181 (16), 135 (70), 105 (34), 91 (100); HRMS (FAB) $C_{37}H_{47}N_2O_4Si$ [*M* + H]$^+$ requires 611.3305, found 611.3305.

Synthesis of amino amide 20. To a solution of the Weinreb amide derived from ester **18** (300 mg, 0.492 mmol) in methanol (5 cm^3) was added 20% $Pd(OH)_2$/C (300 mg), the flask was flushed with argon before being stirred under an atmosphere of hydrogen for 12 hours. The reaction mixture was filtered through a layer of Celite and concentrated under reduced pressure. The residue was chromatographed on silica gel [DCM : MeOH (50 : 1)] to give the amino amide **20** (210 mg, 100%) as an oil. R_f [DCM : MeOH (10 : 1)] 0.12; spectroscopic data were in good agreement with those reported above.

Conversion to pyrrolidinone 23. A solution of amino amide **20** (100 mg, 0.234 mmol) in MeOH (3 cm^3) was heated to reflux and held at reflux for 24 hours. The solution was cooled and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [DCM : MeOH (50 : 1)] to give pyrrolidinone **23** (62 mg, 72%) as a white solid; R_f [DCM : MeOH (10 : 1)] 0.30; mp 110–112 °C; $[\alpha]_D$ +11.30 (*c* 0.2, $CHCl_3$) (70% ee); ν_{max} (neat)/cm^{-1} 3385, 2931, 1682, 1427; δ_H (250 MHz, $CDCl_3$) 7.66–7.25 (10H, m, Ar*H*), 6.20 (1H, br s, N*H*), 4.61 (1H, ddd, *J* 10.4, 7.0, 4.2, C(4)*H*OH), 3.95 (1H, dd, *J* 10.5, 5.8, CH_AH_BOTBDPS), 3.81 (1H, dd, *J* 10.5, 4.8, CH$_A$$H_B$OTBDPS), 3.78 (1H, dt, *J* 10.4, 5.5, C(5)*H*), 3.29 (1H, br s, O*H*), 2.68 (1H, dd, *J* 17.3, 7.0, C(3)H_CH_D), 2.41 (1H, dd, *J* 17.3, 4.2, C(3)H_CH_D), 1.05 (9H, s, ^tBu); δ_C (62.9 MHz) 176.0 (C), 135.4 (CH), 135.3 (CH), 132.4 (C), 132.2 (C), 130.0 (CH), 128.0 (CH), 68.2 (CH), 63.0 (CH_2), 59.2 (CH), 40.3 (CH_2), 26.7 (CH_3), 19.0 (C); *m*/*z* (FAB) 370 ([M + H]$^+$, 59%), 292 (34), 234 (37), 214 (66), 199 (80), 135 (94), 105 (46); HRMS (FAB) $C_{21}H_{28}NO_3Si$ [*M* + H]$^+$ requires 370.1838, found 370.1838.

***Via* amino ester 24.** To a solution of β-hydroxy ester **18** (270 mg, 0.451 mmol) in methanol (5 cm^3) was added 20% $Pd(OH)_2$/C (270 mg), the flask was flushed with argon before being stirred under an atmosphere of hydrogen for 12 hours. The reaction mixture was filtered through a layer of Celite and concentrated under reduced pressure. The residue was chromatographed on silica gel [DCM : MeOH (50 : 1)] to give the amino ester **24** (186 mg, 100%) as an oil.

Ethyl (3R,4R)-5-tert-butyldiphenylsilyloxy-4-amino-3-hydroxypentanoate ***24***. R_f [DCM : MeOH (10 : 1)] 0.20; $[\alpha]_D$ −11.1 (*c* 1.2, $CHCl_3$) (70% ee); ν_{max} (neat)/cm^{-1} 3363, 2932, 2888, 1724, 1426; δ_H (250 MHz, $CDCl_3$) 7.76–7.06 (10H, m, Ar*H*), 4.22 (2H, q, *J* 7.0, OC$H_2$$CH_3$), 3.78–3.47 (5H, br m, C(3)*H*OH + C(5)H_2 + NH_2), 3.10–3.00 (1H, m, C(4)*H*), 2.65 (1H, dd, *J* 15.0, 3.2, C(2)H_AH_B), 2.30 (1H, dd, *J* 15.0, 8.9, C(2)H_AH_B), 1.31 (3H, t, *J* 7.0, OCH$_2$CH_3), 1.13 (9H, s, ^tBu); δ_C (50.3 MHz) 169.9 (C), 134.7 (CH), 132.2 (CH), 131.3 (C), 129.9 (C), 128.9 (CH), 128.0 (CH), 126.9 (CH), 64.7 (CH), 61.5 (CH), 60.1 (CH_2), 59.9 (CH_2), 45.6 (CH_2), 25.5 (CH_3), 18.2 (C), 14.9 (CH_3); *m*/*z* (FAB) 416 ([M + H]$^+$, 100%), 199 (20), 142 (7), 135 (38), 105 (12), 95 (11); HRMS (FAB) $C_{23}H_{34}NO_4Si$ [*M* + H]$^+$ requires 416.2257, found 416.2252.

A solution of amino ester **24** (186 mg, 0.448 mmol) in MeOH (4 cm^3) was heated to reflux and held at reflux for 24 hours. The solution was cooled and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel gel [DCM : MeOH (50 : 1) to give pyrrolidinone **23** (130 mg, 78%) as an oil. R_f [DCM : MeOH (10 : 1)] 0.30; all spectroscopic data were identical to those obtained from the cyclisation of the Weinreb amide derived from ethyl ester **18**.

(4*R*,5*R*)-2-*tert*-Butyldiphenylsilyloxymethylpyrrolidin-3-ol 25. To a solution of pyrrolidinone **23** (120 mg, 0.330 mmol) in THF (5 cm^3) at 0 °C was added BH_3·THF complex (4.95 cm^3, 1.0 M in THF, 4.95 mmol). The solution was stirred at 0 °C until effervescence ceased and then stirred at reflux for 24 hours. Methanol (*ca.* 5 cm^3) was added cautiously to the cooled (0 °C) reaction mixture. The resulting mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel [DCM : MeOH (50 : 1)] to give the pyrrolidine **25** (105 mg, 86%) as a white solid. R_f [DCM : MeOH (10 : 1)] 0.25; mp 100–101 °C; $[\alpha]_D$ +8.5 (*c* 0.5, $CHCl_3$) (70% ee); δ_H (250 MHz, $CDCl_3$) 7.69–7.60 (4H, m, Ar*H*), 7.52–7.25 (6H, m, Ar*H*), 6.20 (1H, s, N*H*), 4.56 (1H, ddd, *J* 11.4, 6.5, 4.5, C(3)*H*OH), 4.52–4.51 (1H, br s, O*H*), 4.23 (1H, dd, *J* 11.2, 4.8, C$H_A$$H_B$OTBDPS), 4.20 (1H, dd, *J* 11.2, 8.0, CH$_A$$H_B$OTBDPS) 3.59 (1H, ddd, *J* 11.4, 8.0, 4.8, C(2)*H*), 3.06 (1H, ddd, *J* 12.7, 7.6, 6.0, C(5)H_EH_F), 2.97 (1H, ddd, *J* 12.7, 6.5, 4.5, C(5)H_EH_F), 2.19 (1H, ddt, *J* 16.1, 6.0, 4.5, C(4)H_CH_D), 1.94 (1H, ddt, *J* 16.1, 7.6, 6.5, C(4)H_CH_D), 1.08 (9H, s, ^tBu); δ_C (62.9 MHz) 135.5 (CH), 135.3 (CH), 131.6 (C), 131.2 (C), 130.3 (CH), 128.0 (CH), 73.8 (CH), 69.0 (CH), 60.3 (CH_2), 52.8 (CH_2), 32.5 (CH_2), 26.8 (CH_3), 19.0 (C); *m*/*z* (FAB) 356 ([M + H]$^+$, 65%), 278 (26), 197 (53), 183 (22), 135 (100); HRMS (FAB) $C_{21}H_{30}NO_2Si$ [*M* + H]$^+$ requires 356.2046, found 356.2043.

Methyl (2*S*)-2-(*N*,*N*-dibenzylamino)-3-benzyloxypropanoate 28

Synthesis of methyl ester hydrochloride salt. Acetyl chloride (2.20 cm^3, 30.8 mmol) was added dropwise to methanol (24 cm^3) at 0 °C. The mixture was stirred for 15 min and L-*O*-benzylserine (2.00 g, 10.3 mmol) was then added portionwise to the solution. The resulting mixture was heated to reflux and held at reflux for 3 hours. Concentration under reduced pressure provided the methyl ester hydrochloride salt (2.25 g, 96%) as a solid.

Methyl (2S)-2-amino-3-benzyloxypropanoate·hydrochloride salt. Mp 162–164 °C (methanol); $[\alpha]_D$ +15.2 (*c* 1.4, MeOH); δ_H (250 MHz, D_2O) 7.37–7.26 (5H, m, Ar*H*), 4.57 (1H, d, *J* 12.0, OC$H_E$$H_F$Ph), 4.47 (1H, d, *J* 12.0, OCH$_E$$H_F$Ph), 4.28 (1H, br t, *J* 3.7, C(2)*H*), 3.93 (1H, dd, *J* 11.0, 4.2, C(3)H_AH_B), 3.83 (1H, dd, *J* 11.0, 3.0, C(3)H$_A$$H_B$), 3.71 (3H, s, O*Me*); δ_C (62.9 MHz) 169.0 (C), 137.1 (C), 129.1 (CH), 128.9 (CH), 128.8 (CH), 73.5 (CH_2), 66.7 (CH_2), 54.1 (CH_3), 53.5 (CH); *m*/*z* (FAB) 210 ([M + H]$^+$, 95%), 196 (8), 150 (5), 120 (10), 102 (10), 91 (100); HRMS (FAB) $C_{11}H_{16}NO_3$ [*M* + H]$^+$ requires 210.1130, found 210.1133.

Conversion to *N*,*N*-dibenzyl protected methyl ester 28. To a solution of the methyl ester (2.00 g, 8.71 mmol) in anhydrous acetonitrile (30 cm^3) was added anhydrous potassium carbonate (5.55 g, 43.6 mmol) followed by benzyl bromide (2.38 cm^3, 21.8 mmol). The mixture was stirred at room temperature for 24 hours. H_2O (50 cm^3) was added and the aqueous phase was extracted with EtOAc (3 × 30 cm^3). The combined organic phases were washed with brine (100 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane : EtOAc (10 : 1)] to

View Article Online

Published on 26 March 2002. Downloaded by University of Western Ontario on 28/10/2014 10:15:46.

give protected methyl ester **28** (3.20 g, 94%) as a colourless oil. R_f [hexane : EtOAc (4 : 1)] 0.60; $[\alpha]_D$ −48.5 (*c* 1.07, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3062, 3028, 2948, 2855, 1735, 1602, 1494, 1453; δ_H (250 MHz, $CDCl_3$) 7.41–7.21 (15H, m, Ar*H*), 4.52–4.30 (2H, m, OCH_EH_FPh), 3.96 (2H, d, *J* 13.9, $NCH_XH_YPh \times 2$), 3.89 (1H, t, *J* 2.8, C(2)*H*), 3.85–3.79 (1H, m, $C(3)H_AH_B$), 3.78 (3H, s, O*Me*), 3.75–3.68 (1H, m, $C(3)H_AH_B$), 3.72 (2H, d, *J* 13.9, $NCH_XH_YPh \times 2$); δ_C (62.9 MHz) 171.8 (C), 139.5 (C), 137.9 (C), 128.6 (CH), 128.2 (CH), 128.1 (CH), 127.4 (CH), 126.9 (CH), 73.0 (CH_2), 69.4 (CH_2), 60.8 (CH), 55.2 (CH_2), 51.2 (CH_3); *m*/*z* (FAB) 390 ($[M + H]^+$, 15%), 330 (32), 282 (8), 268 (41), 181 (9), 91 (100); HRMS (FAB) $C_{25}H_{28}NO_3$ $[M + H]^+$ requires 390.2069, found 390.2070.

(2*SR*)-2-(*N*,*N*-Dibenzylamino)-3-benzyloxypropanoic acid 29

To a solution of the ester **28** (300 mg, 0.771 mmol) in THF (8 cm^3) was added a slurry of $LiOH{\cdot}H_2O$ (194 mg, 4.63 mmol) in H_2O (2 cm^3). The mixture was heated to reflux and held at reflux for 4 hours. The solution was cooled to room temperature, water (15 cm^3) was added and the mixture was acidified to pH 3 with 1 M HCl. The aqueous phase was extracted with Et_2O (3 × 15 cm^3). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to give acid **29** (288 mg, 100%). R_f [hexane : EtOAc (4 : 1)] 0.13; ν_{max} (neat)/cm^{-1} 4059, 3067, 3028, 2923, 2854, 1715, 1495; δ_H (250 MHz, $CDCl_3$) 7.67–7.03 (15H, m, Ar*H*), 4.63 (1H, d, *J* 11.9, OCH_EH_FPh), 4.55 (1H, d, *J* 11.9, OCH_EH_FPh), 4.17 (1H, dd, *J* 10.3, 4.6, $C(3)H_AH_B$), 4.06 (2H, d, *J* 13.3, $NCH_XH_YPh \times 2$), 4.01–3.67 (2H, m, $C(3)H_AH_B$ + C(2)*H*), 3.94 (2H, d, *J* 13.3, $NCH_XH_YPh \times 2$); δ_C (62.9 MHz) 171.1 (C), 137.5 (C), 135.8 (C), 129.2 (CH), 128.7 (CH), 128.4 (CH), 128.1 (CH), 127.8 (CH), 127.2 (CH), 73.4 (CH_2), 67.5 (CH_2), 61.5 (CH), 55.1 (CH_2); *m*/*z* (FAB) 376 ($[M + H]^+$, 100%), 330 (16), 286 (31), 240 (12) 181 (20), 91 (91); HRMS (FAB) $C_{24}H_{26}NO_3$ $[M + H]^+$ requires 376.1913, found 376.1914.

Ethyl (4*SR*)-5-benzyloxy-4-(*N*,*N*-dibenzylamino)-3-oxopentanoate 31

To a solution of acid **29** (300 mg, 0.825 mmol) in THF (8 cm^3) was added 1,1′-carbonyldiimidazole (404 mg, 2.49 mmol). The solution was stirred at room temperature for 2 hours to generate imidazolide **30**. Meanwhile to a solution of LiHMDS (2.49 cm^3, 1.0 M in THF, 2.49 mmol) at −78 °C was added ethyl acetate (0.240 cm^3, 2.49 mmol) and the solution stirred for 20 min. The solution of imidazolide **30** in THF was added *via* cannula and the solution stirred at −78 °C for 30 min then warmed to 0 °C over a period of 1 hour. The mixture was stirred at 0 °C for 1 hour before being quenched with saturated aqueous NH_4Cl (20 cm^3). The aqueous phase was extracted with DCM (3 × 20 cm^3). The combined organic phases were washed with brine (30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane : EtOAc (10 : 1)] to give the β-keto ester **31** (340 mg, 92%) as a pale yellow oil. R_f [hexane : EtOAc (4 : 1)] 0.53; ν_{max} (neat)/cm^{-1} 3062, 3029, 2081, 2926, 2860, 1744, 1716, 1494, 1453; δ_H (250 MHz, $CDCl_3$) 7.43–7.22 (15H, m, Ar*H*), 4.62 (1H, d, *J* 12.0, OCH_EH_FPh), 4.55 (1H, d, *J* 12.0, OCH_EH_FPh), 4.14 (2H, q, *J* 7.2, OCH_2CH_3), 4.01 (1H, dd, *J* 9.2, 6.5, $C(5)H_AH_B$), 3.94 (1H, dd, *J* 9.2, 4.0, $C(5)H_AH_B$), 3.85 (2H, d, *J* 13.1, $NCH_XH_YPh \times 2$), 3.75–3.65 (1H, m, C(4)*H*), 3.73 (1H, d, *J* 16.0, $C(2)H_CH_D$), 3.70 (2H, d, *J* 13.1, $NCH_XH_YPh \times 2$), 3.54 (1H, d, *J* 16.0, $C(2)H_CH_D$), 1.23 (3H, t, *J* 7.2, OCH_2CH_3); δ_C (62.9 MHz) 202.7 (C), 167.3 (C), 138.9 (C), 137.9 (C), 128.9 (CH), 128.5 (CH), 128.3 (CH), 127.5 (CH), 127.1 (CH), 126.8 (CH), 73.4 (CH_2), 66.1 (CH), 65.4 (CH_2), 61.0 (CH_2), 55.0 (CH_2), 46.5 (CH_2), 13.9 (CH_3); *m*/*z* (FAB) 446 ($[M + H]^+$, 100%), 356 (39), 330 (53), 240 (22), 196 (17), 132 (9), 106 (37), 91 (97); HRMS (FAB) $C_{28}H_{32}NO_4$ $[M + H]^+$ requires 446.2331, found 446.2332.

Ethyl (3*SR*, 4*SR*)-5-benzyloxy-4-(*N*,*N*-dibenzylamino)-3-hydroxypentanoate 32

To a solution of β-keto ester **31** (80 mg, 0.18 mmol) in Et_2O (4 cm^3) and MeOH (2 cm^3) was added acetic acid (*ca.* 0.5 cm^3) until the solution was pH 4. The solution was cooled to 0 °C and sodium cyanoborohydride (60 mg, 1.4 mmol) was added. Once effervescence ceased the solution was warmed to room temperature and stirred for 8 hours. The solution was quenched by the addition of a saturated solution of NH_4Cl (15 cm^3) and the aqueous phase was extracted with DCM (3 × 15 cm^3). The combined organic phases were washed with brine (20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane : EtOAc (6 : 1)] to give the amino alcohol **32** (72 mg, 90%) as an oil. R_f [hexane : EtOAc (4 : 1)] 0.38; ν_{max} (neat)/cm^{-1} 3371, 2936, 1726, 1452; δ_H (250 MHz, $CDCl_3$) 7.43–7.19 (15H, m, Ar*H*), 4.59 (1H, d, *J* 12.0, OCH_EH_FPh), 4.52 (1H, d, *J* 12.0, OCH_EH_FPh), 4.19 (1H, ddd, *J* 11.2, 8.5, 3.6, C(3)*H*OH), 4.14 (2H, q, *J* 7.2, OCH_2CH_3), 4.05 (2H, d, *J* 13.2, $NCH_XH_YPh \times 2$), 3.80 (1H, dd, *J* 10.2, 5.5, $C(5)H_AH_B$), 3.69 (1H, dd, *J* 10.2, 4.8, $C(5)H_AH_B$), 3.53 (2H, d, *J* 13.2, $NCH_XH_YPh \times 2$), 3.47 (1H, s, O*H*), 2.80–2.72 (1H, m, C(4)*H*), 2.50 (1H, dd, *J* 15.4, 3.6, $C(2)H_CH_D$), 2.37 (1H, dd, *J* 15.4, 8.5, $C(2)H_CH_D$), 1.23 (3H, t, *J* 7.2, OCH_2CH_3); δ_C (62.9 MHz) 172.0 (C), 138.8 (C), 137.8 (C), 129.0 (CH), 128.4 (CH), 127.7 (CH), 127.5 (CH), 127.1 (CH), 73.2 (CH_2), 66.3 (CH_2), 65.7 (CH_2), 61.3 (CH), 60.4 (CH), 54.3 (CH_2), 39.45 (CH_2), 14.0 (CH_3); *m*/*z* (FAB) 448 ($[M + H]^+$, 20%), 330 (19), 326 (5), 210 (2), 181 (4), 91 (100); HRMS (FAB) $C_{28}H_{34}NO_4$ $[M + H]^+$ requires 448.2488, found 448.2489.

Acknowledgements

We thank the EPSRC (GR/L60166/01 to K.S.C.) for support.

References

1 R. J. Nash, A. E. Bell, G. W. J. Fleet, R. H. Jones and M. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1985, 738.
2 L. D. Hohenschutz, E. A. Bell, P. J. Jewess, D. P. Leworthy, R. J. Pryce, E. Arnold and J. Clardy, *Phytochemistry*, 1981, **20**, 811.
3 A. M. Schofield, P. Witham, R. J. Nash, G. C. Kite and L. E. Fellows, *Comp. Biochem. Physiol.*, 1995, **112A**, 187.
4 A. M. Schofield, L. E. Fellows, R. J. Nash and G. W. J. Fleet, *Life Sci.*, 1986, **39**, 645.
5 (*a*) J. Furukawa, S. Okuda, K. Saito and S.-I. Hatanaka, *Phytochemistry*, 1985, **24**, 593; (*b*) R. J. Nash, E. A. Bell and J. M. Williams, *Phytochemistry*, 1985, **24**, 1620.
6 (*a*) A. D. Elbein, M. Mitchell, B. A. Stanford, L. E. Fellows and S. V. Evans, *J. Biol. Chem.*, 1984, **259**, 12409; (*b*) S. V. Evans, L. E. Fellows and E. A. Bell, *Biochem. Syst. Ecol.*, 1985, **13**, 271; (*c*) A. Welter, J. Jadot, G. Dardenne, M. Marlier and J. Casimir, *Phytochemistry*, 1976, **15**, 747; (*d*) absolute stereochemistry: G. W. Fleet and P. W. Smith, *Tetrahedron*, 1987, **43**, 971.
7 N. Dell'Uomo, M. C. DiGiovanni, D. Misiti, G. Zappia and G. Delle Monache, *Tetrahedron: Asymmetry*, 1996, **7**, 181.
8 *N*-Hydroxyethyl derivative of CYB-3 as biosynthetic precursor for castanospermine and australine: R. J. Molyneux, Y. T. Pan, J. E. Tropea, M. Benson, G. P. Kaushal and A. D. Elbein, *Biochemistry*, 1991, **30**, 9981.
9 G. Ceulemans, A. Van Aerschot, J. Rozenski and P. Herdewijn, *Tetrahedron*, 1997, **53**, 14957.
10 (*a*) Reaction with (allyl)$B(Ipc)_2$: L. M. Mascavage, Q. Lu, J. Vey, D. R. Dalton and P. J. Carroll, *J. Org. Chem.*, 2001, **66**, 3621; (*b*) reaction with allyl bromide/$CrCl_2$: Y Aoyagi, H. Inaba, Y. Hiraiwa, A. Kuroda and A. Ohta, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3975.
11 A. Barco, S. Benetti, C. De Risi, G. P. Pollini, R. Romagnoli and V. Zanirato, *Tetrahedron Lett.*, 1996, **37**, 7599.
12 (*a*) C. Herdeis, H. P. Hubmann and H. Lotter, *Tetrahedron: Asymmetry*, 1994, **5**, 119; (*b*) D. Griffart-Brunet and N. Langlois, *Tetrahedron Lett.*, 1994, **35**, 119.
13 (*a*) B. M. Malle, I. Lundt and R. H. Furneaux, *J. Carbohydr. Chem.*, 2000, **19**, 573; (*b*) A. G. H. Wee, D. D. McLeod and T. J. Rankin, *Heterocycles*, 1998, **48**, 2263.
14 C. M. Huwe and S. Blechert, *Synthesis*, 1997, 61.

View Article Online

15 A. N. Hulme, C. H. Montgomery and D. K. Henderson, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1837.
16 A. N. Hulme and E. M. Rosser, *Org. Lett.*, 2002, **4**, 265.
17 (*a*) M. T. Reetz, *Chem. Rev.*, 1999, **99**, 1121; (*b*) M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1531.
18 (*a*) With isoleucine derived aldehyde: M. T. Reetz, M. W. Drewes, A. Schmitz, X. Holdgrun, T. Wunsch and J. Binder, *J. Philos. Trans. R. Soc. London A*, 1988, **326**, 573; (*b*) with dimethyl tartrate derived aldehyde: H. Ina and C. Kibayashi, *J. Org. Chem.*, 1993, **58**, 52.
19 A. N. Hulme, and C. H. Montgomery, unpublished results.
20 J. M. Andrés and R. Pedrosa, *Tetrahedron*, 1998, 5607.
21 P. Compain and O. R. Martin, *Bioorg. Med. Chem.*, 2001, **9**, 3077.
22 S. Hanessian, H. K. Huynh, G. V. Reddy, G. McNaughton-Smith, B. Ernst, H. C. Kolb, J. Magnani and C. Sweeley, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2803.
23 (*a*) E. Dechaux, P. Savay, S. Bouyain, C. Monneret and J.-C. Florent, *J. Carbohydr. Chem.*, 2000, **19**, 485; (*b*) K. Dax, M. Ebner, R. Peinsipp and A. E. Stütz, *Tetrahedron Lett.*, 1997, **38**, 225.
24 R. V. Hoffmann and J. Tao, *J. Org. Chem.*, 1997, **62**, 2292 and references cited therein.
25 M. T. Reetz, M. W. Drewes, B. R. Matthews and K. Lennick, *J. Chem. Soc., Chem. Commun.*, 1989, 1474.
26 This result is somewhat surprising as a two-step synthesis of acid **29** from *O*-benzylserine (i. BnBr; ii. KOH) has been reported to occur without racemisation; M. T. Reetz, M. W. Drewes, K. Lennick, A. Schmitz and X. Holdgrün, *Tetrahedron: Asymmetry*, 1990, **1**, 375. However, experimental details for this conversion have not been reported.
27 S. Chansrasekhar, Ch. R. Reddy and R. J. Rao, *Tetrahedron*, 2001, **57**, 3435.

Published on 26 March 2002. Downloaded by University of Western Ontario on 28/10/2014 10:15:46.