ARTICLE

OBC
www.rsc.org/obc

Stereoselective tetrapyrido[2,1-*a*]isoindolone synthesis *via* carbanionic and radical intermediates: a model study for the Tacaman alkaloid D/E ring fusion †

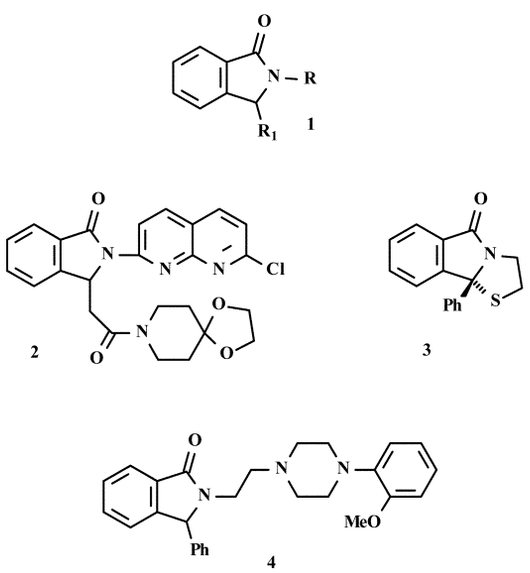
Roger Hunter * and Philip Richards
Department of Chemistry, University of Cape Town, Rondebosch 7701, Cape Town, South Africa. E-mail: Roger@science.uct.ac.za; Fax: +27(21) 6897499; Tel: +27(21) 6502544

Received 20th March 2003, Accepted 6th May 2003
First published as an Advance Article on the web 27th May 2003

Cyclization under both radical and carbanionic conditions of *N*-substituted 3-phenylsulfanylisoindolin-1-one **14** containing a chiral *N*-tether incorporating an enoate ester as the acceptor leads to tetrahydropyrido[2,1-*a*]-isoindolones stereoselectively. The major product **17** from carbanionic cyclization was stereoselectively desulfurized with nickel boride allowing correlation of cyclization products from both methodologies. The cyclization stereoselectivities have been rationalised using a transition-state model in which the acceptor grouping adopts a pseudoaxial configuration. This contrasts with other 6-*exo*-*trig* processes in which a pseudoequatorial configuration is normally adopted, and has been attributed to the steric influence imposed by the bulky *tert*-butyldiphenylsilyloxy chiral auxiliary allylic to the enoate ester. The product stereochemistries provide models for the required *cis*-stereochemistry of the D/E ring fusion of the Tacaman alkaloid skeleton *via* the relatively unexplored C-3-C-14 bond disconnection.

Introduction

The 3-substituted 2,3-dihydro-1*H*-isoindol-1-one structural unit **1** (= 3-substituted isoindolinone or phthalimidine) is a common motif found in both natural products and synthetic pharmaceuticals with biological activity, with examples including the anxiolytic pazinaclone **2**,[1] the non-nucleoside HIV-reverse transcriptase inhibitor **3**[2] and the 5-HT antagonist **4**.[3]



Methodologies for the synthesis of **1** generally[4] fall into two categories. The first entails construction of the five-membered ring from a suitably functionalised benzenoid precursor with concomitant incorporation of the 3-substituent, and the most popular strategy for this involves aryl–benzylic connection *via* an organometallic intermediate,[5] such as in the Parham protocol[6] or using Pd(0) chemistry.[7] In the second, and arguably more commonly encountered approach, 3-substitution is carried out on an existing five-membered ring such as a phthalimide[8] or phthalimidine derivative. Regarding the latter, both carbanionic[9] and carbocationic[10] (acyliminium) intermediates have received widespread attention. By comparison, radical-based approaches,[11] have received far less attention. Recently we reported[12] that a seemingly stable, and thus poorly reactive benzyl radical with a chiral *N*-tethered chain bearing an enoate acceptor chain underwent stereoselective radical cyclization to afford a substituted tetrahydropyrido[2,1-*a*]-isoindolone. The reaction was used as a model for the Tacaman alkaloid ring system in which the desired *cis*-D/E ring junction stereochemistry was achieved using a single allylic stereogenic centre. The cyclization was also extended to the carbanion generated from the α-sulfanyl lactam with LDA. In this paper we disclose details of these reactions as well as the scope for extending these ideas to construction of benzylic tertiary aza centres (Fig. 1).

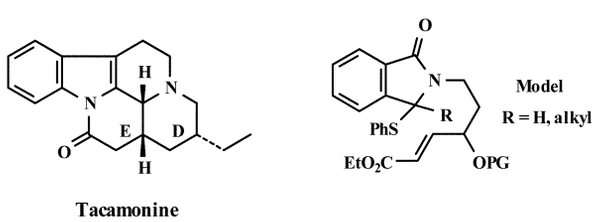


Fig. 1 Tacamonine and the radical cyclization precursor.

Results and discussion

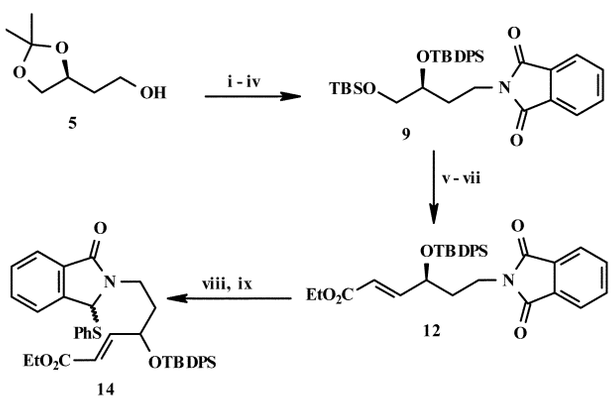
In the original study,[13] the chiral tether was derived from D-ribose. The two stereogenic centres were *cis*-allylic and homoallylic to the enoate ester in the six-membered pseudo-chair transition state, and were considered to have opposing effects in controlling which chair conformation predominated. It was thus rationalised that a desirable cyclization precursor to study was one involving a single allylic stereogenic centre in the tether, and retrosynthetic analysis revealed malic acid to be an

† Electronic supplementary information (ESI) available: Experimental details for compounds **21**–**23**. See http://www.rsc.org/suppdata/ob/b3/b303031h/

DOI: 10.1039/b303031h

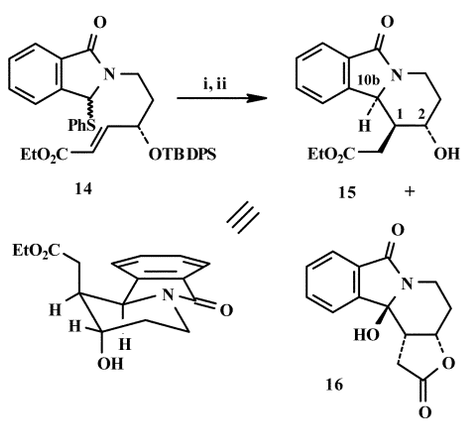
 This journal is © The Royal Society of Chemistry 2003

appropriate starting material for its synthesis. Choice of starting material was further influenced by the availability of methodology for elegant chemodifferentiation of the two carboxyl functionalities *via* an assisted reduction developed by Saito *et al*.[14] To that end, treatment of dimethyl malate with borane dimethyl sulfide together with catalytic borohydride furnished a dihydroxy ester which was protected as its ketal and reduced with lithium aluminium hydride to the known alcohol **5**.[14] Mitsunobu reaction of **5** with phthalimide to **6** followed by conventional ketal hydrolysis to **7** and chemoselective disilylation gave **9** *via* the mono *tert*-butyldimethylsilyl (TBS) ether **8**. Monitoring of enantio-integrity in the series was achieved by converting alcohol **8** to its Mosher's ester **8a**, which by ^{1}H NMR analysis relative to the diastereomeric mixture of Mosher's esters from racemic **8** proved to be 100% enantiopure. Compound **9** was chemoselectively deprotected (TBS) to **10**, oxidized to **11** and olefinated with ethoxycarbonylmethylene-triphenylphosphorane in dichloromethane exclusively to the *E*-enoate ester **12** with no trace[15] of any *Z*-isomer unlike the ribose series. Finally, conventional chemoselective imide carbonyl reduction with borohydride to **13** followed by promoted sulfanylation with thiophenol[9b,13,16] and boron trifluoride etherate produced the target α-sulfanyl lactam **14**. All steps in the synthesis were high yielding (> 85% per step), and easy to carry out so that gram quantities of radical precursor **14** could be obtained, (Scheme 1).



Scheme 1 *Reagents and conditions*: i, phthalimide, DEAD, PPh_3, THF; ii, HCl (1 M), THF, Δ; iii, TBSCl, imid, CH_2Cl_2; iv, TBDPSCl, imid, CH_2Cl_2, DMF; v, HF (40%), CH_3CN; vi Swern oxidation; vii PPh_3=$CHCO_2Et$, CH_2Cl_2; viii, $NaBH_4$, THF, −40 °C; ix, PhSH (2 eq.), BF_3·Et_2O (2 eq.), CH_2Cl_2, −78 °C.

The scene was now set for radical cyclisation studies. α-Acylamino radical cyclizations have proven to be a versatile methodology for *N*-heterocycle synthesis following pioneering work by Hart[11] and co-workers in the 1980's. Exposure of **14** to standard[17] radical cyclization conditions (Bu_3SnH–AIBN (cat) in refluxing toluene) resulted in rapid conversion to a more polar product in essentially quantitative yield (97%). This result contrasts with our previous study involving a ribose-derived tether in which cyclization was much slower and the yield of the major product much lower (~60%), presumably as a result of ring strain imposed by the acetonide protecting group. The radical cyclization in the present study was relatively insensitive to concentration effects and no reduced product was ever observed, indicating a fast cyclization step. Scrutiny of the crude product by 400 MHz ^{1}H NMR revealed it to be a mixture of cyclized diastereomers (approximated as 4 : 2 : 1 : 1) based on the loss of the olefinic resonances as well as the appearance of four new doublets for H-10b. Furthermore, the vicinal coupling constants (in order as J = 3.7, 11.1, 11.1, 3.5 Hz) indicated the major diastereomer to have a *cis* relationship between the H-10b and H-1 hydrogens, with the ethoxycarbonylmethylene substituent consequently axial. This followed as a result of H-10b being obligatorily axial in view of the high degree of sp^2 character in the five-membered ring resulting in a *trans* ring junction as established by Beckwith *et al.*[18] for a series of related compounds. Analysis of the cyclization mixture by TLC suggested a difficult chromatographic separation. Thus, the mixture was desilylated with TBAF in THF to produce two compounds separable by column chromatography. The yield of the major component (53%) was consistent (approximating the 4 : 8 ratio from NMR) with formation from desilylation of the major component of the crude cyclization mixture. NMR analysis established it as the cyclized diastereomer **15** with the hydroxyl and ethoxycarbonylmethylene groups *trans* on the basis of a small vicinal coupling constant for H-1/H-2 indicating a *gauche* relationship, as well as H-2 being assigned as equatorial (small vicinal couplings to 2 × H-3). The absolute stereochemistry and conformation could be established as shown in Scheme 2. Failure of **15** to form a lactone with TBAF corroborated the assignment. The minor product **16** (19%) gave an unexpected result. Its infrared spectrum (ν_{CO} = 1785 cm^{-1}) coupled with a downfield signal (δ = 5.06 ppm) for H-2 (numbering shown) indicated a lactone and thus a *cis*-disposition between the C-1 and C-2 substituents. The absence of a proton signal for H-10b and the presence of a hydroxyl group suggested that benzylic (C-10b) hydroxylation had taken place to an α-hydroxylactam. Finally, the structure was unambiguously established as **16** by a single crystal X-ray structure determination, (Scheme 2, Fig. 2).



Scheme 2 *Reagents and conditions*: i, Bu_3SnH (3eq.), AIBN (cat), toluene / Δ; ii, TBAF, THF.

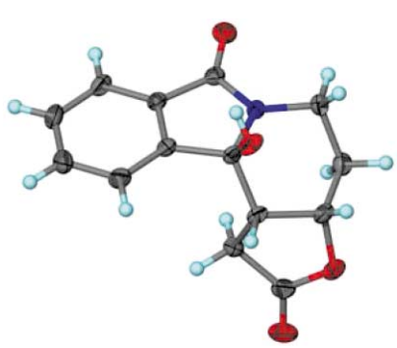


Fig. 2 X-Ray crystal structure of **16**.

Precedence in the literature exists for this type of oxidation in which tetraalkylammonium salts are known to promote allylic oxidation with oxygen *via* catalyzing the breakdown of the hydroperoxide intermediate.[19] In this case, fluoride-promoted benzylic deprotonation to a dienolate followed by reaction with oxygen would satisfactorily account for hydroperoxide formation.

Certain aspects of the stereoselectivity of cyclization are noteworthy. In keeping with other radical cyclizations, the initial cyclization product leading to **15** must be that of kinetic control in view of it being a higher energy diastereomer.

Its formation is striking in that it implies the radical acceptor to be in a pseudoaxial configuration in the chair-like transition state. This is in contrast to the known preference in other 6-*exo* cyclizations[20] for the side chain to be pseudoequatorial, including the major product from our previous research on isoindolone formation using an adjacent isopropylidene ketal as the stereo-directing auxiliary. A transition-state model based on the stereoselectivity observed reveals that formation of **15** proceeds *via* approach of the sterically unencumbered radical from the face of the enoate ester proximal to the chiral auxiliary in order to minimise steric interaction between the ethoxycarbonylmethylene and OTBDPS groups.

The observed configuration at C-1 indicates that the enoate ester grouping adopts an *endo* orientation with respect to the isoindolone ring, also in order to minimise steric strain with the bulky OTBDPS group, resulting in a trans C1/2 relationship in the product. As the six-membered ring begins to take shape, the acceptor chain adopts a pseudoaxial configuration, (Fig. 3) leading to **15**.

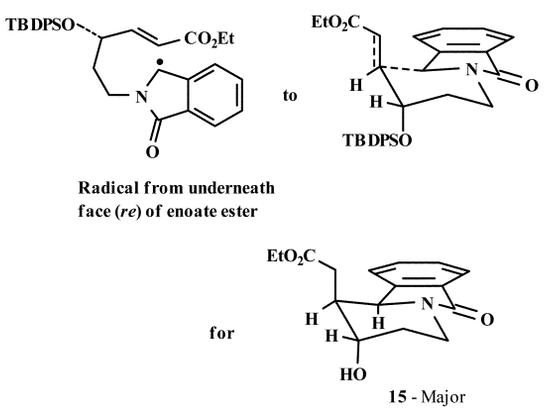


Fig. 3 Transition-state model for cyclization to **15**.

Rationalization of formation of the minor product **16** is more complex in view of the oxidation step, which presumably occurred during the TBAF deprotection *via* a dienolate.[19] Formation of **16** could have arisen from either of two of the four diastereomeric products in the crude mixture with the ethoxycarbonylmethylene group in the α-position. Fig. 4 depicts the transition state for formation of **16** *via* the cyclized diastereomer that is desilylated with cyclization to the lactone, and oxidized with retention of configuration at C-10b. As with formation of **15**, it also implies a pseudoaxial configuration for the acceptor side chain in the transition state. In this case, the steric implications of having the C-1/C-2 substituents *cis* is offset by the more favourable placing of the OTBDPS group as pseudoequatorial, as well as the radical approaching *anti* to the silyloxy group, (Fig. 4). However, the isolated yield of 19% suggests that formation of **16** may well have occurred from both of the diastereomers previously mentioned. These results reveal a

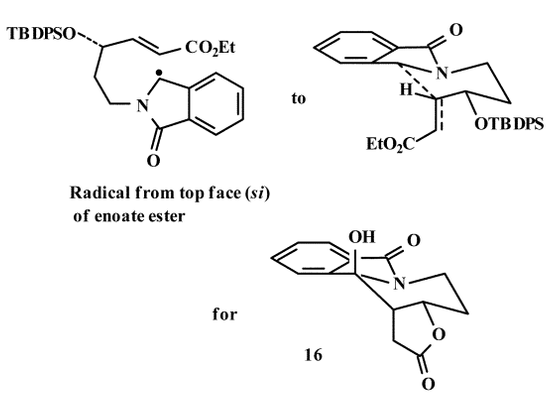
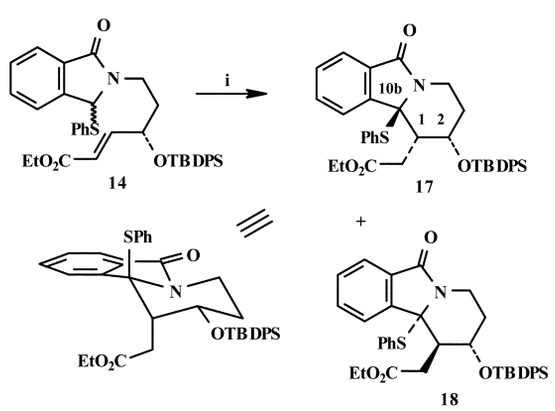


Fig. 4 Transition-state model for cyclization to **16**.

strong stereo-directing bias imposed by the silyloxy group,[21] which can override the preference of the acceptor side chain to be in a pseudoequatorial configuration.

The diastereoselectivity of the radical cyclization was pleasing in that the *cis*-relationship between the benzylic H-10b and the hydrogen at C-1 of **15** corresponds to the correct ring junction stereochemistry found in the Tacaman alkaloids (see Tacamonine[22] in Fig. 1), suggesting an equivalent study to prepare indolo[2,3-*a*]quinolizidines is worth pursuing. The desired outcome would necessitate that expanding the radical-containing ring to six-members and changing the phenyl to an indolo group retains the stereochemical preference. Furthermore, this result contrasts with the *trans* preference obtained from cyclization in the ribose-tethered series involving two stereo-directing centres. Presumably in the latter case, the ketal auxiliary didn't exert as powerful a steric influence as the silyloxy group in the present study.

We next turned our attention to studying carbanionic cyclization in view of the presence of carbonyl and phenylsulfanyl stabilizing groups. Precedence for this type of reaction existed in the work of Luzzio and Zacherl[9e] who had demonstrated a similar system to undergo sodium hydride-promoted cyclization. We were further encouraged when it was discovered that desilylation of **14** using TBAF indeed promoted cyclization *via* Michael addition to the enoate ester, with incorporation of the phenylsulfanyl group in the product, unlike the radical series. In order to optimise diastereoselectivity, the conditions were changed to using LDA (3eq.) at low temperature (−78°), which produced the two *anti* diastereomers **17** and **18** in 77% and 18% yield respectively after column chromatography. Stereochemical assignment of **17** was made on the basis of vicinal coupling constants and assignment of H-2 as axial ($J_{2/3}$ = 11.7 Hz). Once again, a pseudoaxial configuration for the phenylsulfanyl group is obligatory in view of the requirement for the N–$C_{carbonyl}$ and C_{ring}–C_{ring} attachment bonds of the five-membered ring to be virtually coplanar, (Scheme 3). Rationalisation of the diastereoselectivity is again dominated by the observation that both products **17** and **18** indicate a pseudoaxial configuration for the Michael acceptor at C-1 in the transition state *via* an *endo* approach of the enoate ester *wrt* to the isoindolyl ring. In this case, in contrast to the radical cyclization, the dominant product **17** was formed by attacking the enoate ester from the distal face to the bulky OTBDPS group in order to minimise the dominant SPh–OTBDPS interaction.



Scheme 3 *Reagents and conditions*: i, LDA (3 eq.), THF, −78 °C; **17** : **18** = 77 : 18.

This is at the expense of the ethoxycarbonylmethylene–OTBDPS interaction, which is minimized *via* an *endo* approach of the enoate ester to set up a *cis* C-1/C-2 relationship, (Fig. 5).

The minor component **18** arises from attack of the double bond from the more hindered face proximal to the silyloxy group, with some compensation from the *endo* orientation of the enoate ester resulting in a *trans* C1/2 relationship. Once

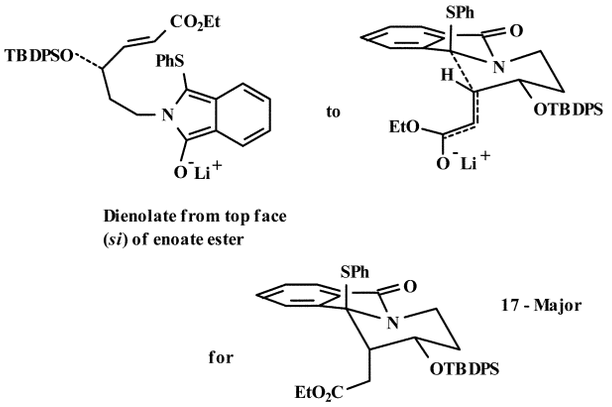
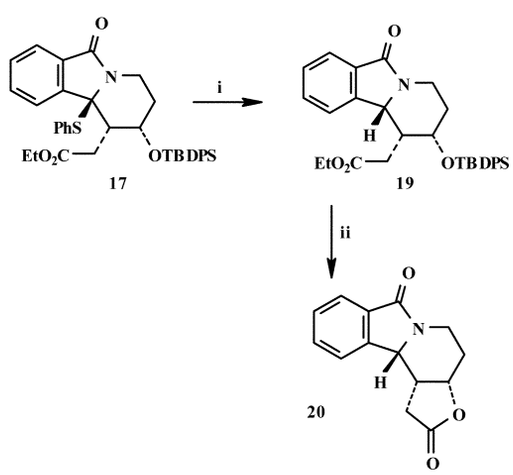


Fig. 5 Transition-state model for carbanionic cyclization to **17**.

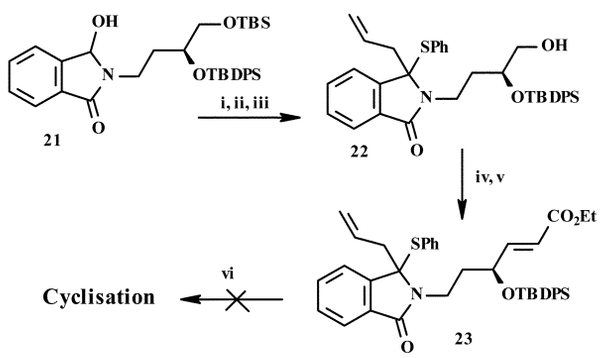
again, the acceptor adopts a pseudoaxial configuration as a result of the steric influence imposed by the bulky silyloxy group in the cyclization.

Several methods were screened for reductive desulfurization of the major diastereomer **17**, with nickel boride[23] proving to be the most efficient. Thus treatment of **17** with nickel boride derived from treating nickel (II) chloride with sodium borohydride returned a 92% yield of reduced isoindolone **19** with retention of configuration at the benzylic centre, presumably so as to retain the OTBDPS group in an equatorial configuration. Synthesis of compound **19** thus offers a complementary route to the radical cyclization approach (to **15**) for setting up the C-1 and C-10b hydrogens as *cis* for the Tacaman D/E ring junction stereochemistry, and as the alternative diastereoisomer. Desilylation of **19** with HF in acetonitrile resulted in deprotection and cyclization to the lactone **20**, thus vindicating the configurational assignments of the C-1/2 substituents in compound **17**, (Scheme 4).



Scheme 4 *Reagents and conditions*: i, Ni boride, aq. EtOH, rt; ii, HF, CH_3CN, 45 °C.

A further aspect explored was to investigate the possibility of quaternizing the isoindolone benzylic position.[6c,7a–e,9a–c,24] To this end α-sulfanylisoindolone **17** was selected for modification since it provided opportunity to explore the use of various sulfur-based methodologies. Disappointingly, none of the standard methods based on intermolecular allylation methodology (substitution of sulfur) resulted in efficient benzylic allylation. The various methods tried included: transmetallation with lithium di-*tert*-butylbiphenylide[25] followed by quenching with allyl bromide; Lewis acid ($BF_3{\cdot}Et_2O$, $SnCl_4$, TMSOTf, $TiCl_4$) / allyltrimethylsilane; allyltributyltin.[16a,26] In each case, several products were obtained due to multiple allylation or significant quantities of starting material was recovered. Similarly, treatment of lactone **20** (Scheme 4) with LDA (1 eq., −78 °C, THF) followed by reaction with allyl bromide (excess) resulted in benzylic allylation as well as allylation α to the lactone carbonyl group at low conversion. Since intermolecular allylation appeared to be too sterically demanding and that the ester functionality was interfering with some of the methods, it was decided to allylate prior to cyclization so that an intramolecular process could be studied. Thus imide **9** (Scheme 1) was reduced to α-hydroxy lactam **21**, which could be sulfanylated as before and efficiently allylated *via* its carbanion, generated using *n*-butyllithium. Chemoselective removal of the TBS ether to **22** with subsequent elaboration as before provided the enoate ester cyclization precursor **23**. Exposure of **22** to standard radical cyclization conditions resulted in an inseparable mixture of products. ^{1}H NMR analysis suggested that reductive cleavage of the sulfide was one of the reactions that had taken place, *via* reduction of the intermediate radical. A similar tendency of a tertiary radical to prefer reduction over C–C bond formation has been noted by Hart and co-workers,[11a] (Scheme 5).



Scheme 5 *Reagents and conditions*: i, PhSH (2eq.), $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C; ii; *n*-BuLi, THF, −78 °C; allyl bromide to rt; iii, HF, CH_3CN; iv, Swern oxidation, v, PPh_3=$CHCO_2Et$, CH_2Cl_2, vi, Bu_3SnH, AIBN (cat), Tol, 100 °C.

Desulfurization of **23** and intramolecular carbanionic cyclisation remained as a possibility but this was not studied.

In conclusion, we have effectively developed model systems for the *cis* D/E Tacamonine ring junction stereochemistry, and uncovered a novel expression of *6-exo-trig* radical cyclization stereoselectivity. Further work is in progress attempting to translate these ideas to alkaloid synthesis.

Experimental

All solvents were freshly distilled. Tetrahydrofuran, benzene and toluene were distilled under nitrogen from sodium wire, while dichloromethane was distilled over phosphorus pentoxide. Benzophenone was used as an indicator with THF.

All chromatography was carried out using petroleum ether and ethyl acetate as eluents. Column chromatography was performed using silica gel 60 (Merck 7734; 70–230 Mesh ASTM). Thin layer chromatography (TLC) was carried out on aluminium-backed Merck silica gel 60 F_{254} plates. Compounds were viewed on the plates by using a UV lamp, or by spraying with a 2.5% solution of anisaldehyde in a mixture of sulfuric acid and ethanol (1 : 10 v/v) and then heating at 150 °C. The organic layers of reactions subjected to extractive work-up were dried by stirring with magnesium sulfate followed by filtration.

Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrometer in dichloromethane. These spectra were recorded from 4000 to 600 cm^{-1} on sodium chloride plates. High-resolution nuclear magnetic resonance spectra were recorded on a Varian Unity 400 (at 399.951 MHz for ^{1}H and 100.579 MHz for ^{13}C) and were carried out in $CDCl_3$ unless otherwise stated. Chemical shifts (δ) were recorded using residual chloroform (δ = 7.24 in ^{1}H NMR and δ = 77.00 in ^{13}C NMR) or tetramethylsilane as an internal standard. The

residual DMSO peak (δ = 39.52 in ^{13}C NMR) was used as an internal standard for D_6-DMSO solutions.

Optical rotations were obtained using a Perkin Elmer 141 polarimeter at 20 °C. The concentration *c* refers to g 100 ml^{-1}.

Melting points were obtained using a Reichert Jung hot stage microscope and are uncorrected. Elemental analyses were performed using a Fisons EA 1108 CHN elemental analyser. HRMS were recorded on a VG70-SEQ Micromass instrument. All reagents were purchased from Aldrich or Merck. Low temperature reactions were carried out using dry ice in acetone for the low temperature cooling baths.

Synthesis of radical precursor 14

(*S*)-2,2-Dimethyl-4-(2-phthalimidoethyl)-1,3-dioxolane 6. Alcohol **5** (0.43 g, 2.97 mmol) was dissolved in tetrahydrofuran (10 ml) with stirring under nitrogen. Phthalimide (0.57 g, 3.9 mmol) and triphenylphosphine (1.03 g, 3.9 mmol) were then added and the solution cooled to 0 °C. Diethyl azodicarboxylate (0.62 ml, 3.9 mmol) was added dropwise. The reaction was allowed to warm to room temperature and on completion (TLC), the solvent was evaporated and the residue dissolved in dichloromethane, which was washed with potassium hydroxide (1 M). The organic layer was dried, the solvent evaporated and the residue chromatographed (20% ethyl acetate–petroleum ether) to afford **6** as a colourless crystalline solid (0.77 g, 2.79 mmol, 94%). Mp 44–46 °C (ethyl acetate–hexane); $[\alpha]_D = +10.6°$ (*c* = 1.0, $CHCl_3$) (Found: C, 65.57; H, 6.31; N, 5.28%. $C_{15}H_{17}NO_4$ requires C, 65.44; H, 6.22; N, 5.09%); ν_{max}/cm^{-1} 3057, 2986, 1775, 1716, 1398; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, isopropylidene-Me), 1.34 (3H, d, isopropylidene-Me), 1.90 (2H, m, H-1′), 3.56 (1H, dd, *J* 6.7, 7.8 Hz, H-5), 3.81 (2H, m, H-2′), 4.07 (1H, dd, *J* 5.9, 7.8 Hz, H-5), 4.14 (1H, m, H-4), 7.70 (2H, m, aromatic), 7.83 (2H, m, aromatic); δ_C (100 MHz, $CDCl_3$) 25.5, 26.8 (2 × isopropylidene-Me), 32.3 (C-1′), 35.1 (C-2′), 69.1 (C-5), 73.9 (C-4), 109.0 (C-2), 123.1, 132.1, 133.8 (aromatic), 168.2 (C=O); *m*/*z* 260.092 (M^+–CH_3. $C_{14}H_{14}NO_4$ requires *M*, 260.0923).

(*S*)-4-Phthalimido-1,2-butanediol 7. The imide **6** (0.32 g, 1.16 mmol) was dissolved in a mixture of tetrahydrofuran (3 ml) and hydrochloric acid (3 ml, 1 M) and heated at 60 °C for 30 minutes. Aqueous sodium hydrogen carbonate was added and the tetrahydrofuran removed on a rotary evaporator. The aqueous phase was extracted with 3 portions of ethyl acetate, and the organic layers combined, dried and evaporated to a residue. This was subjected to flash chromatography (80% ethyl acetate–petroleum ether) to obtain diol **7** as a colourless solid (0.23 g, 0.98 mmol, 85%). Mp 105–106 °C (ethyl acetate–petroleum ether); $[\alpha]_D = -29.9°$ (*c* = 1.0, $CHCl_3$) (Found: C, 61.45; H, 5.31; N, 5.86%. $C_{12}H_{13}NO_4$ requires C, 61.23; H, 5.57; N, 5.95%); ν_{max}/cm^{-1} 3581, 3061, 2963, 1775, 1707, 1396; δ_H (400 MHz, $CDCl_3$) 1.75 (2H, m, H-3), 2.40 (1H, br s, OH), 3.46 (1H, dd, *J* 7.2, 11.2 Hz, H-4), 3.58 (1H, dd, *J* 3.2, 11.2 Hz, H-4), 3.58 (1H, br s, OH), 3.65 (1H, m, H-2), 3.86 (2H, dd, *J* 5.6, 7.6 Hz, H-1), 7.70-7.84 (4H, m, aromatic); δ_C (100 MHz, $CDCl_3$) 32.0 (C-3), 34.4 (C-4), 66.4 (C-1), 69.1 (C-2), 123.4 & 132.0 & 134.1 (aromatic), 168.9 (C=O); *m*/*z* 235.0820 (M^+. $C_{12}H_{13}NO_4$ requires *M*, 235.0844).

(*S*)-4-Phthalimido-1-(*tert*-butyldimethylsilyloxy)butan-2-ol 8. The diol **7** (3.14 g, 13.36 mmol) was dissolved in dichloromethane (60 ml) with stirring under nitrogen. Imidazole (1.00 g, 14.7 mmol) was added and the solution cooled to 0 °C. *Tert*-butyldimethylsilyl chloride (2.02 g, 13.4 mmol) was added and the solution allowed to warm to room temperature overnight. Water was added and the mixture extracted with three portions of dichloromethane. The organic layers were combined, dried, and evaporated to a residue. This was chromatographed (20% ethyl acetate–petroleum ether) to afford **8** as a colourless oil (4.52 g, 12.93 mmol, 97%). $[\alpha]_D = -3.9°$ (*c* = 1.0, $CDCl_3$); ν_{max}/cm^{-1} 3597, 3048, 2955, 1775, 1713, 1398; δ_H (400 MHz, $CDCl_3$) 0.06 (6H, s, CH_3), 0.89 (9H, s, *t*-butyl CH_3), 1.80 (2H, m, H-3), 2.65 (1H, br s, OH), 3.49 (1H, dd, *J* 6.7, 10.0 Hz, H-4), 3.63 (1H, dd, *J* 3.9, 10.0 Hz, H-4), 3.68 (1H, m, H-2), 3.88 (2H, m, H-1), 7.70–7.86 (4H, m, aromatic); δ_C (100 MHz, $CDCl_3$) –5.4 (2 × CH_3), 18.3 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 31.9 (C-3), 34.9 (C-4), 67.0 (C-2), 69.5 (C-1), 123.2 & 132.2 & 133.9 (aromatic), 168.5 (C=O); *m*/*z* 334.1472 (M^+-CH_3. $C_{18}H_{27}NO_4Si$ requires *M*, 334.1474).

Mosher's ester (*S*)-1-(*tert*-butyldimethylsilyl)oxy-4-phthalimido-2-butyl 2-(*R*)-2-trifluoromethyl-2-methoxy-2-phenylethanoate, 8a. For monitoring of enantio-integrity, the alcohol **8** (0.030 g, 0.086 mmol) and (*R*)-methoxytrifluoromethylphenylacetic acid (0.030 g, 0.13 mmol) were stirred in dichloromethane (2 ml) at 0 °C. DMAP (5 mg, cat.) and DCC (0.027 g, 0.13 mmol) were added and the reaction was warmed to room temperature. After 2 hours, TLC indicated completion of reaction, thus solvent was evaporated to leave a residue which was diluted in ether, filtered, and the residue washed with ether. The filtrate was concentrated and the residue chromatographed (20% ethyl acetate–petroleum ether) to give the product as a colourless oil (0.041 g, 0.073 mmol, 85%, 100% *ee* by ^{1}H NMR relative to a sample from racemic **8**). $[\alpha]_D = +9.1°$ (*c* = 1.0, $CHCl_3$); ν_{max}/cm^{-1} 2955, 2858, 1774, 1748, 1714, 1469, 1398; δ_H (400 MHz, $CDCl_3$) 0.01 (6H, s, CH_3), 0.83 (9H, s, *t*-butyl CH_3), 2.07 (1H, m, H-3), 2.18 (1H, m, H-3), 3.59 (3H, s, OCH_3), 3.69 (1H, dd, *J* 4.6, 11.2 Hz, H-1), 3.77 (3H, m, 2 × H-4, H-1), 5.12 (1H, m, H-2), 7.40 (3H, m, aromatic) 7.59 (2H, m, aromatic), 7.71 (2H, aromatic), 7.84 (2H, m, aromatic); δ_C(100 MHz, $CDCl_3$) −5.7 (2 × CH_3), 18.1 ($C(CH_3)_3$), 25.7 ($C(CH_3)_3$), 29.5 (C-3), 34.3 (C-4), 55.4 (OMe), 63.1 (C-1), 74.9 (C-2), 121.9 (*C*OMe), 123.3 (aromatic), 124.7 (CF_3), 127.6 & 128.4 & 129.5 & 132.1 & 132.2 & 134.0 (aromatic), 166. 2 & 168.1 (C=O); *m*/*z* 566 (M^+ + H, 3%), 508 (M^+–$C(CH_3)_3$, 45), 332.2 (100).

(*S*)-4-Phthalimido-2-(*tert*-butyldiphenylsilyl)oxy-1-(*tert*-butyldimethylsilyl)oxybutane 9. To a solution of alcohol **8** (4.52 g, 12.93 mmol) in dichloromethane (50 ml) under a nitrogen atmosphere was added dimethylformamide (5 ml), imidazole (1.00 g, 14.7 mmol) and *tert*-butyldiphenylsilyl chloride (3.50 ml, 13.5 mmol). The mixture was stirred at room temperature until TLC indicated that the starting material had been consumed. Water was added and the mixture extracted with 3 portions of dichloromethane. The organic layers were combined and dried, then evaporated to give a residue that was chromatographed (10% ethyl acetate–petroleum ether) to remove dimethylformamide. The product fraction was evaporated to a residue (7.62 g) contaminated with *tert*-butyldiphenylsilyl alcohol (TBDPSOH). The product **9** and this contaminant eluted at the same R_f. The contaminant could easily be separated from the product **10** of the next step by chromatography so the mixture was not purified further. For characterisation purposes a portion of pure **10** was reprotected using the same procedure that was used to obtain **8** to give compound **9** free of TBDPSOH. $[\alpha]_D = +19.0°$ (*c* = 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3057, 2933, 1771, 1715; δ_H (400 MHz, $CDCl_3$) −0.12, and −0.07 (6H, s, TBDMS CH_3), 0.81 (9H, s, *t*-butyl CH_3), 1.07 (9H, s, *t*-butyl CH_3), 1.90 (1H, m, H-3), 2.03 (1H, m, H-3), 3.53 (2H, d, *J* 5.9 Hz, H-1), 3.78 (3H, m, H-2, 2 × H-4), 7.30–7.85 (14H, m, aromatic); δ_C (100 MHz, $CDCl_3$) −5.6 (TBDMS 2 × CH_3), 18.2 & 19.3 ($C(CH_3)_3$), 25.8 & 27.0 ($C(CH_3)_3$), 32.6 (C-3), 34.4 (C-4), 65.6 (C-), 71.8 (C-), 123.0 & 127.5 & 127.6 & 129.5 & 129.6 & 132.4 & 133.7 & 133.8 & 134.3 & 135.8 & 135.9 (aromatic), 168.2 (C=O); *m*/*z* (EI) 572 (M^+ − CH_3, 1%), 530 (M^+ − $C(CH_3)_3$, 100%), 271 (31), 209 (42), 135 (19).

(*S*)-4-Phthalimido-2-(*tert*-butyldiphenylsilyl)oxy-1-butanol 10. In a polypropylene container was placed a solution of the

mixture of the disilyl ether **9** and TBDPSOH in acetonitrile (12 ml) at room temperature. To this solution was added 40% hydrofluoric acid (2.5 ml) and the reaction monitored by TLC until the starting material had been consumed. The mixture was neutralized with aqueous sodium hydrogen carbonate and extracted with three portions of dichloromethane. The combined organic layers were dried and evaporated to a residue, which was chromatographed (20% ethyl acetate–petroleum ether) to give alcohol **10** (5.45 g, 11.52 mmol, 89% over 2 steps). $[\alpha]_D$ = +51.4° (*c* = 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3571, 3056, 2938, 1777, 1715, 1397; δ_H (400 MHz, $CDCl_3$) 1.08 (9H, s, *t*-butyl CH_3), 1.85 (1H, br s, OH), 1.94 (2H, m, H-3), 3.67 (4H, m, H-1 and H-4), 3.82 (1H, m, H-2), 7.31–7.79 (14H, m, aromatic); δ_C (100 MHz, $CDCl_3$) 19.2 ($C(CH_3)_3$), 27.0 ($C(CH_3)_3$), 32.6 (C-3), 34.4 (C-4), 65.4 (C-2), 71.7 (C-1), 123.1 & 127.6 & 127.7 & 129.7 & 129.8 & 132.1 & 133.2 & 133.7 & 133.8 & 135.6 & 135.8 (aromatic), 168.1 (C=O); *m*/*z* 442.1826 ($M^+ - CH_2OH$. $C_{27}H_{28}NO_3Si$ requires *M*, 442.1838).

(*S*)-4-Phthalimido-2-(*tert*-butyldiphenylsilyl)oxy-1-butanal 11. Dimethyl sulfoxide (1.73 ml, 24 mmol) was dissolved in dry dichloromethane and cooled to −78 °C under nitrogen. Oxalyl chloride (1.45 ml, 16.6 mmol) was then added, and after 15 minutes the alcohol **10** (5.25 g, 11.08 mmol) was slowly added in a solution of dichloromethane. After a further 5 minutes, triethylamine (7.8 ml, 55 mmol) was added and the mixture was slowly allowed to warm to 0 °C. The reaction was quenched by adding aqueous sodium carbonate and extracted with three portions of dichloromethane. The combined organic layers were dried and evaporated to give crude **11**, which could be taken on to the next step. For characterisation purposes a small portion was chromatographed (20% ethyl acetate–petroleum ether) and subjected to high vacuum for 24 hours to remove traces of dimethyl sulfide, to give aldehyde **11** as a colourless gum. $[\alpha]_D$ = +23.9° (*c* = 1.1, $CHCl_3$); ν_{max}/cm^{-1} 3061, 2938, 1779, 1716, 1400; δ_H (400 MHz, $CDCl_3$) 1.13 (9H, s, *t*-butyl CH_3), 2.05 (2H, m, H-3), 3.76 (2H, m, H-4), 4.13 (1H, td, *J* 0.9, 5.6, 5.6 Hz, H-2), 7.38 (6H, m, aromatic), 7.70 (6H, m, aromatic), 7.84 (2H, m, aromatic), 9.65 (1H, d, *J* 0.9 Hz, H-1); δ_C (100 MHz, $CDCl_3$) 19.3 ($C(CH_3)_3$), 26.9 ($C(CH_3)_3$), 31.4 (C-3), 33.6 (C-4), 76.1 (C-2), 123.2 & 127.9 & 130.1 & 132.2 & 132.6 & 132.7 & 133.9 & 135.8 (aromatic), 168.0 (C=O), 202.6 (C-1); *m*/*z* 414.1172 ($M^+ - C(CH_3)_3$. $C_{24}H_{20}NO_4Si$ requires *M*, 414.1161).

Ethyl (2*E*,4*S*)-4-(*tert*-butyldiphenylsilyl)oxy-6-phthalimidohex-2-enoate 12. The crude aldehyde **11** was dissolved in dichloromethane and ethoxycarbonylmethylenetriphenylphosphorane (4.2 g, 12 mmol) was added. The mixture was stirred at room temperature and monitored by TLC. When the reaction was complete the solvent was evaporated and the residue chromatographed directly (20% ethyl acetate–petroleum ether) to obtain enoate ester **12** (5.78 g, 10.66 mmol, 96% over 2 steps) as a colourless gum. $[\alpha]_D$ = +34.0° (*c* = 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3058, 2989, 1777, 1714, 1663, 1398; δ_H (400 MHz, $CDCl_3$) 1.11 (9H, s, *t*-butyl CH_3), 1.27 (3H, t, CH_2CH_3), 1.87 (2H, m, H-5), 3.67 (2H, m, H-6), 4.13 (2H, m, CH_2CH_3), 4.42 (1H, m, H-4), 6.01 (1H, dd, *J* 1.5, 15.6 Hz, H-2), 6.92 (1H, dd, *J* 5.3, 15.6 Hz, H-3), 7.30–7.83 (14H, m, aromatic); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_2CH_3), 19.3 ($C(CH_3)_3$), 27.0 ($C(CH_3)_3$), 33.5 (C-5), 35.3 (C-6), 60.3 (CH_2CH_3), 70.5 (C-4), 121.3 (C-2), 123.1, 127.6, 127.7, 129.7, 129.8, 132.2, 133.1, 133.4, 133.8, 135.8, 135.8, 135.8 (aromatic), 148.3 (C-3), 166.2 & 168.0 (C=O); *m*/*z* 484.1592 ($M^+ - C(CH_3)_3$. $C_{28}H_{26}NO_5Si$ requires *M*, 484.1580).

Ethyl (2*E*,4*S*)-6-(1,3-dihydro-3-hydroxy-1-oxoisoindol-2-yl)-4-(*tert*-butyldiphenylsilyl)oxyhex-2-enoate 13. To a solution of **12** (3.91 g, 7.22 mmol) in tetrahydrofuran (20 ml) and methanol (50 ml) at −40 °C was added sodium borohydride (1.13 g, 30.0 mmol). The reaction was kept below −20 °C and was monitored by TLC. When the starting material had been consumed the reaction was *carefully* quenched with aqueous ammonium chloride and the methanol removed by evaporation. The aqueous phase was extracted with three portions of dichloromethane and the combined organic layers were dried, and evaporated to give the crude product. This was then chromatographed (40% ethyl acetate–petroleum ether) to give **13** as a foam (3.61 g, 6.64 mmol, 2 epimers, 92.0%). ν_{max}/cm^{-1} 3056, 2934, 1706, 1683, 1659, 1422; δ_H (400 MHz, $CDCl_3$) 1.07 (9H, s, *t*-butyl CH_3), 1.25, 1.29 (3H, t, CH_2CH_3, 2 epimers), 1.70 (2H, m, H-5), 3.23 (2H, m, H-6), 4.12, 4.16 (2H, m, CH_2CH_3, 2 epimers), 4.33, 4.45 (1H, m, H-4, 2 epimers), 5.20, 5.51 (1H, s, benzylic H, 2 epimers), 5.99 (1H, dd, *J* 1.2, 15.8 Hz, H-2), 6.86 (1H, dd, *J* 5.1, 15.8 Hz, H-3), 7.23–7.68 (14H, m, aromatic); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_2CH_3), 19.3 ($C(CH_3)_3$), 27.0 ($C(CH_3)_3$), 34.7, 35.3, 35.5, 35.7 (C-5, C-6, 2 epimers), 60.4 (CH_2CH_3), 70.5, 70.7 (C-4, 2 epimers), 81.3, 82.4 (benzylic C, 2 epimers), 120.9, 121.1 (C-2, 2 epimers), 123–143 (aromatic), 148.7, 148.8 (C-3, 2 epimers), 166.4, 166.4 & 167.1, 167.1 (C=O, 2 epimers); *m*/*z* 486.1726 ($M^+ - C(CH_3)_3$. $C_{28}H_{28}NO_5Si$ requires *M*, 486.1737).

Ethyl (2*E*,4*S*)-6-(1,3-dihydro-3-phenylsulfanyl-1-oxoisoindol-2-yl)-4-(*tert*-butyldiphenylsilyl)oxyhex-2-enoate 14. The α-hydroxylactam **13** (1.00 g, 1.84 mmol) was dissolved in dry dichloromethane and cooled to −78 °C under nitrogen. $BF_3{\cdot}Et_2O$ (0.47 ml, 3.7 mmol) and benzenethiol (0.38 ml, 3.7 mmol) were added and the solution stirred at −78 °C for 2 hours. The reaction was quenched with aqueous sodium carbonate and extracted with three portions of dichloromethane. The combined organic layers were washed with dilute potassium hydroxide and then dried and evaporated. The crude product was chromatographed (20% ethyl acetate–petroleum ether) to give pure **14** as a gum (1.14 g, 1.78 mmol, 2 epimers, 97%). ν_{max}/cm^{-1} 3054, 2988, 1710, 1697, 1659, 1426; δ_H (400 MHz, $CDCl_3$) 1.10, 1.13 (9H, s, *t*-butyl CH_3, 2 epimers), 1.21, 1.30 (3H, t, CH_2CH_3, 2 epimers), 1.77 (2H, m, H-5), 3.52 (2H, m, H-6), 4.05, 4.20 (2H, m, CH_2CH_3, 2 epimers), 4.50, 4.41 (1H, m, H-4, 2 epimers), 4.98, 5.46 (1H, s, benzylic H, 2 epimers), 5.92 (1H, dd, *J* 1.5, 15.7 Hz, H-2), 6.82 (1H, dd, *J* 5.1, 15.7 Hz, H-3), 6.90–7.75 (19H, m, aromatic); δ_C (100 MHz, $CDCl_3$) 14.2, 14.3 (CH_2CH_3, 2 epimers), 19.3, 19.3 ($C(CH_3)_3$, 2 epimers), 27.0 ($C(CH_3)_3$), 34.9 (C-5), 35.8 (C-6), 60.3, 60.4 (CH_2CH_3, 2 epimers), 65.7, 66.7 (benzylic C, 2 epimers), 70.3, 70.9 (C-4, 2 epimers), 120.7, 121.3 (C-2, 2 epimers), 123–143 (aromatic), 148.5, 148.7 (C-3, 2 epimers), 166.0 & 167.3 (C=O); *m*/*z* 578.1798 ($M^+ - C(CH_3)_3$). $C_{34}H_{32}NO_4SSi$ requires *M*, 578.1821).

Radical cyclization of 14

To a solution of the sulfide **14** (0.46 g, 0.71 mmol) in dry, deoxygenated toluene (30 ml) at 90 °C was added a solution of tributyltin hydride (0.60 ml, 2.2 mmol) and AIBN (15 mg) in toluene (20 ml) dropwise over 30 minutes. The solution was stirred until TLC indicated that no starting material remained. Carbon tetrachloride (1 ml) was then added and the solvent evaporated. The residue was chromatographed (30% ethyl acetate–petroleum ether) to give a band of products as a gum (0.36 g, 0.69 mmol, 97%). ^1H NMR spectral analysis of this crude residue indicated that 4 diastereomers were present in a 4:2:1:1 ratio in order of decreasing chemical shift based on the doublet for H-10b at δ = (5.12, *J* 3.7 Hz; 4.62, *J* 11.1 Hz; 4.44, *J* 11.1 Hz; 4.28, *J* 3.5 Hz).

Deprotection of mixture of cyclization products

The mixture of isomers (0.606 g, 1.15 mmol) was dissolved in tetrahydrofuran (10 ml) and tetrabutylammonium fluoride (1 M) in tetrahydrofuran (4 ml) was added. The mixture was stirred at room temperature and water was added when TLC

indicated that no starting material remained. The tetrahydrofuran was evaporated and the aqueous phase was extracted with three portions of dichloromethane. The combined organic layers were dried and evaporated and the residue chromatographed (80% ethyl acetate–petroleum ether) to give the lactam **15** (0.177 g, 0.63 mmol, 53%) as a colourless crystalline solid. A band of mixed products was also isolated. This mixture was purified by recrystallization (ethyl acetate–petroleum ether) to give a minor product as a colourless crystalline solid identified as **16** using X-ray crystallography (0.057 g, 0.22 mmol, 19%).

Major product: (1*S*,2*S*,10b*S*)-1,2,3,10b-tetrahydro-1-ethoxycarbonylmethyl-2-hydroxypyrido[2,1-*a*]isoindol-6(4*H*)-one 15. Mp 123–125 °C (ethyl acetate–petroleum ether); $[\alpha]_D = -15.3°$ (c = 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3608, 3059, 2994, 1732, 1679, 1431; δ_H (400 MHz, $CDCl_3$) 1.03 (3H, t, CH_2CH_3), 1.66 (1H, dd, J 6.7, 16.3 Hz, H-1a), 1.73 (1H, dd, J 7.0, 16.3 Hz, H-1a), 1.78 (2H, m, H-3), 2.66 (1H, br s, OH), 3.03 (1H, m, H-1), 3.39 (1H, ddd, J 5.8, 11.6, 13.0 Hz, H-4), 3.81 (2H, m, CH_2CH_3), 4.19 (1H, m, H-2), 4.27 (1H, ddd, J 2.2, 5.2, 13.0 Hz, H-4), 5.03 (1H, d, J 4.0 Hz, H-10b), 7.36 (1H, d, J 7.8 Hz, H-10), 7.47 (2H, m, aromatic), 7.88 (1H, d, J 7.6 Hz, H-7); δ_C (100 MHz, $CDCl_3$) 13.9 (CH_2CH_3), 27.0 (C-3), 30.7 (C-1a), 33.9 (C-4), 40.2 (C-1), 55.9 (C-10b), 60.6 (CH_2CH_3), 67.8 (C-2), 122.8 & 123.9 & 128.2 & 131.0 & 133.4 & 143.2 (aromatic), 166.7 & 172.0 (C=O); m/z 289.1304 (M^+. $C_{16}H_{19}NO_4$ requires M, 289.1314).

Minor product: (3a*S*,11b*S*,11c*R*)-3a,4,5,11c-tetrahydro-11b-hydroxyfuro[3′,2′:3,4]pyrido[2,1-*a*]isoindol-2(1*H*),7(11b*H*)-dione 16. Mp decomposes > 140 °C; $[\alpha]_D = -74.1°$ (c = 0.5, $CHCl_3$); ν_{max}/cm^{-1} 3326, 1785, 1696; δ_H (400 MHz, $CDCl_3$) 1.52 (1H, dd, J 12.2, 17.6 Hz, H-1), 1.59 (1H, m, H-4), 2.00 (1H, dd, J 9.0, 17.6 Hz, H-1), 2.37 (1H, m, H-4), 3.08 (1H, ddd, J 4.1, 10.3, 13.5 Hz, H-5), 3.42 (1H, ddd, J 7.5, 8.8, 12.2 Hz, H-11c), 3.78 (1H, dt, J 5.4, 13.7 Hz, H-5), 4.00 (1H, d, J 3.0 Hz, OH), 5.06 (1H, m, H-3a), 7.40–7.61 (4H, m, aromatic); δ_C (100 MHz, D6-DMSO) 26.4 (C-4), 29.5 (C-1), 31.8 (C-5), 41.7 (C-11c), 75.3 (C-3a), 86.1 (C-11b), 122.2, 122,6, 129.5, 130.9, 132.2, 146.3 (aromatic), 164.6 (C=O), 174.6 (C=O); m/z 259.0832 (M^+. $C_{14}H_{13}NO_4$ requires M, 259.0845).

Carbanionic cyclization

Diisopropylamine (0.80 ml, 5.7 mmol) was added to dry tetrahydrofuran (10 ml) under nitrogen at 0 °C. *n*-Butyllithium (2.15 ml of a 2.5 M solution in hexanes, 5.4 mmol) was then added and the mixture was stirred for 15 minutes. The mixture was then cooled to −78°C and the sulfide **14** (1.14 g, 1.79 mmol) was slowly added as a solution in tetrahydrofuran (5 ml), turning the solution yellow. After 60 minutes the reaction was quenched by adding aqueous sodium hydrogen carbonate and extracted with dichloromethane. The organic layer was dried and evaporated to a residue consisting of 2 products by TLC. These were separated by chromatography (20% ethyl acetate–petroleum ether) to give the less polar major product **17** (0.87 g, 1.37 mmol, 77%) as a colourless, crystalline solid and the more polar minor product **18** (0.20 g, 0.32 mmol, 18%), also as a colourless, crystalline solid.

(1*S*,2*S*,10b*S*)-1,2,3,10b-Tetrahydro-1-ethoxycarbonylmethyl-10b-phenylsulfanyl-2-(*tert*-butyldiphenylsilyl)oxypyrido[2,1-*a*]-isoindol-6(4*H*)-one 17. Mp 126–128 °C (ethyl acetate–petroleum ether); $[\alpha]_D = -190.1°$ (c = 1.0, $CHCl_3$) (Found: C, 71.74; H, 6.69; N, 2.43; S, 4.87. $C_{38}H_{41}NO_4SSi$ requires C, 71.78; H, 6.50; N 2.20; S 5.04%); ν_{max}/cm^{-1} 3055, 2988, 2306, 1733, 1697, 1432; δ_H (400 MHz, $CDCl_3$) 0.99 (3H, t, CH_2CH_3), 1.11 (9H, s, *t*-butyl CH_3), 1.54 (1H, m, H-3), 1.57 (1H, dd, J 8.8, 16.7 Hz, H-1a), 1.74 (1H, m, H-3), 2.73 (1H, dd, J 2.1, 16.7 Hz, H-1a), 3.21 (1H, td, J 4.0, 13.2, 13.3 Hz, H-4), 3.38 (1H, m, H-1), 3.79 (2H, m, CH_2CH_3), 4.24 (1H, ddd, J 1.3, 5.5, 13.3 Hz, H-4), 4.79 (1H, dt, J 4.5, 4.5, 11.7 Hz, H-2), 6.65–7.83 (19H, m, aromatic); δ_C(100 MHz, $CDCl_3$) 13.9 (CH_2CH_3), 19.2 ($C(CH_3)_3$), 27.0 ($C(CH_3)_3$), 29.2 (C-3), 29.3 (C-1a), 34.2 (C-4), 43.8 (C-1), 60.3 (CH_2CH_3), 69.0 (C-2), 78.7 (C-10b), 122.8, 124.3, 127.7, 127.9, 128.2, 128.4, 128.5, 129.2, 129.9, 130.1, 130.9, 131.6, 133.0, 133.9, 135.8, 136.0, 136.0, 144.4 (aromatic), 165.9 & 172.5 (C=O); m/z 526.2410 ($M^+ - SC_6H_5$. $C_{32}H_{36}NO_4Si$ requires M, 526.2414).

(1*R*,2*S*,10b*R*)-1,2,3,10b-Tetrahydro-1-ethoxycarbonylmethyl-10b-phenylsulfanyl-2-(*tert*-butyldiphenylsilyl)oxypyrido[2,1-*a*]-isoindol-6(4*H*)-one 18. Mp 133–135 °C (ethyl acetate–petroleum ether); $[\alpha]_D = +40.7°$ (c = 1.0, $CHCl_3$), (Found: C, 71.87; H, 6.66; N, 2.42; S, 4.98. $C_{38}H_{41}NO_4SSi$ requires: C, 71.78; H, 6.50; N, 2.20; S, 5.04%); ν_{max}/cm^{-1} 3058, 2984, 2307, 1732, 1696, 1427; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, CH_2CH_3), 1.22 (9H, s, *t*-butyl CH_3), 1.45 (2H, m, H-3), 1.55 (1H, dd, J 7.9, 16.1 Hz, H-1a), 1.75 (1H, dd, J 6.2, 16.1 Hz, H-1a), 3.42 (1H, ddd, J 2.3, 6.2, 7.9 Hz, H-1), 3.77 (2H, m, CH_2CH_3), 3.90 (1H, m, H-4), 3.99 (1H, q, J 2.6 Hz, H-2), 4.20 (1H, m, H-4), 6.90 (4H, m, aromatic), 7.05 (1H, m, aromatic), 7.14 (1H, m, aromatic), 7.30 (1H, m, aromatic), 7.42 (7H, m, aromatic), 7.55 (1H, m, aromatic), 7.81 (4H, m, aromatic); δ_C (100 MHz, $CDCl_3$) 13.9 (CH_2CH_3), 19.4 ($C(CH_3)_3$), 27.1 ($C(CH_3)_3$), 27.8 (C-3), 31.1 (C-1a), 34.9 (C-4), 44.5 (C-1), 60.6 (CH_2CH_3), 70.0 (C-2), 76.2 (C-10b), 122.9, 123.9, 127.7, 127.8, 128.0, 128.8, 129.9, 129.9, 130.7, 131.1, 131.4, 133.0, 134.0, 136.0, 136.1, 136.3, 145.5 (aromatic), 165.7 & 171.1 (C=O); m/z 526.2435 ($M^+ - SC_6H_5$. $C_{32}H_{36}NO_4Si$ requires M, 526.2414).

(1*R*,2*S*,10b*R*)-1,2,3,10b-Tetrahydro-1-ethoxycarbonylmethyl-2-(*tert*-butyldiphenylsilyl)oxypyrido[2,1-*a*]isoindol-6(4*H*)-one 19. A two-necked flask was fitted with a condenser, a pressure-equilibrating dropping funnel and a stirrer bar. The system was purged with nitrogen and **17** (0.30 g, 0.47 mmol) was added as a solution in ethanol (150 ml), followed by solid nickel chloride hexahydrate (2.85 g, 12 mmol). When the solution was homogeneous, the dropping funnel was filled with aqueous sodium borohydride (0.90 g, 24 mmol in 10 cm^3 H_2O), which was added dropwise to the green solution of nickel chloride, resulting in an immediate colour change of solution to black. Once the addition was complete, the reaction mixture was refluxed until TLC indicated that no starting material remained. This mixture was filtered through Celite® and the filter cake was washed thoroughly with dichloromethane. The filtrate was evaporated and the residue extracted with dichloromethane. The organic phase was then dried, and evaporated. The final product was purified by flash chromatography (30% ethyl acetate–petroleum ether) to give **19** (0.23 g, 0.43 mmol, 92%) as a colourless, crystalline solid. Mp 102–104 °C (ethyl acetate–petroleum ether); $[\alpha]_D = -97.8°$ (c = 1.0, $CHCl_3$), (Found: C, 72.70; H, 7.22; N, 2.75. $C_{32}H_{37}NO_4Si$ requires C, 72.83; H, 7.07; N, 2.65%); ν_{max}/cm^{-1} 3061, 2990, 2314, 1737, 1698, 1429; δ_H (400 MHz, $CDCl_3$) 0.97 (3H, t, CH_2CH_3), 1.08 (9H, s, *t*-butyl CH_3), 1.56 (1H, dd, J 8.8, 16.5 Hz, H-1a), 1.60 (2H, m, H-3), 2.54 (1H, dd, J 2.4, 16.5 Hz, H-1a), 2.73 (1H, td, J 4.7, 13.4, 13.4 Hz, H-4), 3.19 (1H, m, H-1), 3.63–3.86 (2H, m, CH_2CH_3), 4.12 (1H, dt, J 4.8, 4.8, 10.8 Hz, H-2), 4.28 (1H, d, J 3.5 Hz, H-10b), 4.30 (1H, ddd, J 1.5, 5.7, 13.4 Hz, H-4), 7.30–7.80 (14H, m, aromatic); δ_C (100 MHz, $CDCl_3$) 13.9 (CH_2CH_3), 19.1 ($C(CH_3)_3$), 26.5 (C-3), 26.9 ($C(CH_3)_3$), 29.0 (C-1a), 36.7 (C-4), 40.3 (C-1), 60.2 (C-10b), 60.4 (CH_2CH_3), 71.7 (C-2), 123.5 & 123.7 & 127.7 & 127.8 & 128.3 & 129.9 & 130.0 & 130.8 & 133.3 & 133.4 & 133.8 & 135.8 & 135.9 & 141.7 (aromatic), 166.7 & 172.9 (C=O); m/z 470.1776 ($M^+ - C(CH_3)_3$. $C_{28}H_{28}NO_4Si$ requires M, 470.1788).

(3a*S*,11b*R*,11c*R*)-3a,4,5,11c-Tetrahydrofuro[3′,2′:3,4]pyrido-[2,1-*a*]isoindol-2(1*H*),7(11b*H*)-dione 20. To a solution of **19** (1.58 g, 2.99 mmol) in acetonitrile (6 ml) in a polypropylene container was added 40% hydrofluoric acid in acetonitrile (4 ml) and the mixture stirred for 5 days at 45 °C. Solid sodium

hydrogen carbonate was then added until the effervescence ceased. The mixture was diluted with water and extracted with dichloromethane. The organic layer was dried with magnesium sulfate and evaporated. The crude product was chromatographed (80% ethyl acetate–petroleum ether) to obtain pure **20** (0.66 g, 2.71 mmol, 91%) as a colourless, crystalline solid; Mp 223–226 °C (ethyl acetate–petroleum ether); $[\alpha]_D = +183.0°$ (c = 1.0, $CHCl_3$); ν_{max}/cm^{-1} 3058, 2987, 1780, 1694, 1424; δ_H (400 MHz, $CDCl_3$) 1.67 (1H, dd, J 10.6, 18.1 Hz, H-1), 1.89 (1H, m, H-4), 2.03 (1H, dd, J 9.2, 18.1 Hz, H-1), 2.28 (1H, m, H-4), 3.30 (1H, ddd, J 4.2, 8.4, 13.5 Hz, H-5), 3.42 (1H, m, H-11c), 4.16 (1H, ddd, J 5.1, 7.0, 13.5 Hz, H-5), 4.75 (1H, d, J 4.8, H-11b), 5.02 (1H, td, J 5.1, 7.7, 7.7 Hz, H-3a), 7.37–7.87 (4H, m, aromatic); δ_C (100 MHz, $CDCl_3$) 27.3 (C-4), 27.4 (C-1), 34.9 (C-5), 37.3 (C-11c), 55.7 (C-11b), 75.6 (C-3a), 121.8 & 124.2 & 129.0 & 131.9 & 132.8 & 142.6 (aromatic), 167.2 & 174.5 (C=O); m/z 243.0888 (M^+. $C_{14}H_{13}NO_3$ requires 243.0895).

X-Ray crystal preparation, data collection, processing and structure refinement ‡

A single crystal of **16** ($C_{14}H_{13}NO_4$, M = 259.08) was covered in a small amount of paratone oil and mounted on a glass fibre. X-ray intensity data were collected at 173 K on a Nonius Kappa CCD with 1.5 kW graphite monochromated MoKα-radiation. Refined unit cell parameters: a = 8.375(1), b = 7.653(1), c = 9.691(1) Å, β = 100.634(1)°, V = 610.5(1) Å^3 and Z = 2. The diffraction patterns were indexed with a primitive monoclinic cell. The strategy for the data collection was evaluated using the *Collect* Software.[27] The detector to crystal distance was 40 mm. Data were collected by a phi scan and several omega scans. The data were scaled and reduced using *Denzo-SMN*.[28] Unit cell dimensions were refined on all data. Absorption was negligible (μ(MoKα) = 0.104 mm^{-1}). Of the 5227 reflections measured, 2511 were unique (R_{int} = 0.014). The space group $P2_1$ was chosen on the basis of systematic absences and intensity statistics. The structure was solved and refined using *SHELXL97*.[29] The absolute structure chosen for the final model was based on the known absolute configuration of the starting material. (The Flack parameter value of −0.5(8) indicated that the diffraction data could not distinguish the enantiomers). Hydrogen atoms were placed in calculated positions and included in the model during later stages of the refinement. Plots of the molecular structure were obtained with *ORTEP*[30] and *PLATON*.[31] The programme *X-SEED*,[32] an interface to Shelx, was used during the structure solution and refinements. Final R-factors were R_1 = 0.029, wR_2 = 0.068 for 2318 observed data [$I > 2\sigma(I)$], and S (goodness of fit) = 1.032.

Acknowledgements

We thank the National Research Foundation for financial support, and Dr John Bacsa and Professor Mino Caira for the X-ray determination.

‡ CCDC reference number 208077. See http://www.rsc.org/suppdata/ob/b3/b303031h/ for crystallographic data in .cif or other electronic format.

References

1 M. Suzuki, M. Uchiumi and M. Marasaki, *Psychopharmacology*, 1995, **121**, 442.
2 E. De Clercq, *J. Med. Chem.*, 1995, **38**, 2491.
3 Z. P. Zhuang, M. P. Kung, M. Mu and H. F. Kung, *J. Med. Chem.*, 1998, **41**, 157.
4 For some earlier methods see: T. Noguchi and M. Kawanami, *J. Pharm. Soc., Jpn.*, 1937, **57**, 196; J. H. Helberger, A. V. Rebay and D. B. Hevér, *Liebigs, Ann. Chem.*, 1938, 197; P. Pfeiffer and E. Jainsch, *J. Prakt. Chem.*, 1941, **159**, 241; H. R. Henze and W. J. Leanza, *J. Org. Chem.*, 1952, **17**, 4; G. Caronna and S. Palazzo, *Gazz. Chim. Ital.*, 1953, **83**, 308.
5 J. Clayden, C. J. Menet and D. J. Mansfield, *Org. Lett.*, 2000, **2**, 4229.
6 W. Oppolzer, M. Wills, M. J. Kelly, M. Signer and J. Blagg, *Tetrahedron Lett.*, 1990, **31**, 5015; J. B. Campbell, R. F. Dedinas and S. A. Trumbower-Walsh, *J. Org. Chem.*, 1996, **61**, 6205; M. I. Collado, I. Manteca, N. Sotomayor, M-J. Villa and E. Lete, *J. Org. Chem.*, 1997, **62**, 2080.
7 P. Evans, R. Grigg, M. I. Ramzan, V. Sridharan and M. York, *Tetrahedron Lett.*, 1999, **40**, 3021; N. G. Kundu, M. W. Khan and R. Mukhopadhyay, *Tetrahedron*, 1999, **55**, 12361; M-J. Wu, L-J. Chang, L-M. Wei and C-F Lin, *Tetrahedron*, 99, **55**, 13193; H. Ishibashi, K. Ohata, M. Niihara, T. Sato and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, 2000, 547–553; R. Grigg, V. Savic and V. Tambyrajah, *Tetrahedron Lett.*, 2000, **41**, 3003; C. S. Cho, H. S. Shim, H-J. Choi, T-J. Kim, S. C. Shim and M. C. Kim, *Tetrahedron Lett.*, 2000, **41**, 3891; C. Pays and P. Mangeney, *Tetrahedron Lett.*, 2001, **42**, 589; A. Garcia, D. Rodriguez, L. Castedo, C. Saá and D. Dominguez, *Tetrahedron Lett.*, 2001, **42**, 1903.
8 A. G. Griesbeck, M. Oelgemöller and J. Lex, *Synlett*, 2000, **10**, 1455; E. Deniau and D. Enders, *Tetrahedron Lett.*, 2000, **41**, 2347; Y. Saito, T. Sakamoto and Y. Kikugawa, *Synthesis*, 2001, 221.
9 Y. Terao and M. Sekiya, *Chem. Pharm. Bull.*, 1975, **23**, 184; M. K. Eberle, L. Brzechffa and W. J. Houlihan, *J. Org. Chem.*, 1977, **42**, 894; E. Toja, A. Omodei-Sale and G. Nathansohn, *Tetrahedron Lett.*, 1979, **20**, 2921; P. Beak, S. T. Kerrick and D. J. Gallagher, *J. Am. Chem. Soc.*, 1993, **115**, 10628; F. A. Luzzio and D. P. Zacherl, *Tetrahedron Lett.*, 1998, **39**, 2285; A. Couture, E. Deniau, P. Grandclaudon and C. Hoarau, *J. Org. Chem.*, 1998, **63**, 3128; A. Couture, E. Deniau, P. Grandclaudon and C. Hoarau, *Tetrahedron*, 2000, **56**, 1491; Z. Guo and A. G. Schultz, *J. Org. Chem.*, 2001, **66**, 2154; E. Deniau and D. Enders, *Tetrahedron*, 2001, **57**, 2581.
10 M. Othman, P. Pigeon and B. Decroix, *Tetrahedron*, 1997, **53**, 2495; S. M. Allin, C. J. Northfield, M. I. Page and A. M. Z. Slawin, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1715; M. Othman, P. Pigeon and B. Decroix, *J. Heterocycl. Chem.*, 2001, **38**, 35; S. Marchalin, P. Pigeon, J. Sikoraiova and B. Decroix, *Heterocycles*, 2002, **56**, 129; A. Daich, S. Marchalin, J. Sikoraiova and B. Decroix, *Tetrahedron Lett.*, 2002, **43**, 4747.
11 D. A. Burnett, J. K. Choi, D. J. Hart and Y. M. Tsai, *J. Am. Chem. Soc.*, 1984, **106**, 8201; D. J. Hart and T. K. Yang, *J. Org. Chem.*, 1985, **50**, 235.
12 R. Hunter and P. Richards, *Tetrahedron Lett.*, 2000, **41**, 3755.
13 R. Clauss and R. Hunter, *J. Chem. Soc., Perkin Trans. 1*, 1997, 71.
14 S. Saito, T. Ishikawa, A. Kuroda, K. Koga and T. Moriwake, *Tetrahedron*, 1992, **48**, 4067.
15 S. Valverde, M. Martin-Lomas, B. Herradon and S. Garcia-Ochoa, *Tetrahedron*, 1987, **43**, 1895; R. Clauss, W. Hinz and R. Hunter, *Synlett*, 1997.
16 G. E. Keck and E. J. Enholm, *Tetrahedron Lett.*, 1985, **26**, 3311; N. Hucher, B. Decroix and A. Daiech, *J. Org. Chem.*, 2001, **66**, 4695.
17 T. Okano, T. Sakaida and S. Eguchi, *J. Org. Chem.*, 1996, **61**, 8826; M. Ikeda, J. Shikaura, N. Maekawa, K. Daibuzono, H. Teranishi, Y. Teraoka, N. Oda and H. Ishibashi, *Heterocycles*, 1999, **50**, 31; W. R. Bowman, C. F. Bridge and P. Brookes, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1; W. R. Bowman, M. O. Cloonan and S. L. Krintel, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2885.
18 A. L. J. Beckwith, S. P. Joseph and R. T. A. Mayadunne, *J. Org. Chem.*, 1993, **58**, 4198; A. L. J. Beckwith, S. P. Joseph, R. T. A. Mayadunne and A. C. Willis, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1995, **51**, 1438.
19 C. Anselmi, A. Camparini and M. Scotton, *J. Heterocycl. Chem.*, 1983, **20**, 687; L. J. Csanyi, K. Jaky I. Palinko, A. Rockenbauer and L. Korecz, *Phys. Chem. Chem. Phys.*, 2000, **2**, 3801; L. J. Csanyi and K. Jaky, *Phys. Chem. Chem. Phys.*, 2001, **3**, 2018.
20 M. Ihara, K. Yasui, N. Taniguchi and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1469; M. Koreeda and L. G. Hamaan, *J. Am. Chem. Soc.*, 1990, **112**, 8175; S. D. Burke and J. Rancourt, *J. Am. Chem. Soc.*, 1991, **113**, 2335; K. Ogura, A. Kayano, T. Fujino, N. Sumitani and M. Fujita, *Tetrahedron Lett.*, 1993, **34**, 8313; A. L. J. Beckwith, *Chem. Soc. Rev.*, 1993, 143; A. Martinez-Grau and J. Marco-Contelles, *J. Chem. Soc., Perkin Trans. 1*, 1998, 155; X. Sanchez-Ruiz, C. Jaime and J. Marco-Contelles, *J. Mol. Struct.*, 1998, **471**, 209; G. E. Keck, S. F. McHardy and J. A. Murry, *J. Org. Chem.*, 1999, **64**, 4465; N. Hori, H. Matsukura, G. Matsuo and T. Nakata, *Tetrahedron Lett.*, 1999, **40**, 2811; A. C. Durand, J. Rodriguez and J. P. Dulcère, *Synlett*, 2000, 731; R. Pedrosa, C. Andrés, J. M. Iglesias and M. A. Obeso, *Tetrahedron*, 2001, **57**, 4005; S. N. Joshi, V. G. Puranik, A. R. A. S. Deshmukh and B. M. Bhawal, *Tetrahedron: Asymmetry*, 2001, **12**, 3073.
21 I. Fleming, A. Barbero and D. Walter, *Chem. Rev.*, 1997, **97**, 2063.
22 Recent syntheses of Tacamonine: M. Lounasmaa, K. Karinen, D. Din Belle and A. Tolvanen, *Tetrahedron*, 1998, **54**, 157; M. Suzuki

and M. Ihara, *Heterocycles*, 2000, **52**, 1083; B. Danieli, G. Lesma, D. Passarella, A. Sacchetti and A. Silvani, *Tetrahedron Lett.*, 2001, **42**, 7237; R. Lavilla, O. Coll, J. Bosch, M. Orozco and J. F. Luque, *Eur. J. Org. Chem.*, 2001, **19**, 3719; T. L. Ho and E. Gorobets, *Tetrahedron*, 2002, **58**, 4969.
23 R. B. Boar, D. W. Hawkins, J. F. McGhie and D. H. R. Barton, *J. Chem. Soc., Perkin Trans. 1*, 1973, 654; J. M. Khurana and A. Gogia, *Org. Prep. Proced. Int.*, 1997, **29**, 1.
24 N. A. Jonsson and P. Moses, *Acta Chem. Scand. Ser. B*, 1974, **28**, 225; P. Evans, R. Grigg, M. I. Ramzan, V. Sridharan and M. York, *Tetrahedron Lett.*, 1999, **40**, 3021; A. Padwa and A. G. Waterson, *Tetrahedron*, 2000, **56**, 10159; N. Hucher, B. Decroix and A. Daiech, *J. Org. Chem.*, 2001, **66**, 4695; Z. Li and Y. Zhang, *Tetrahedron*, 2002, **58**, 5301 . For some general methods of preparing amines with quaternary α-carbon centers, see: C. Cativiela and M. D. Diaz-de-Villegas, *Tetrahedron: Asymmetry*, 1998, **9**, 3517; D. Enders and U. Reinhold, *Tetrahedron: Asymmetry*, 1997, **8**, 1895; D. A. Cogan, G. Liu and J. Ellman, *Tetrahedron*, 1999, **55**, 8883; M. J. North, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2209.
25 C. Strohmann, S. Luedtke and O. Ulbrich, *Organometallics*, 2000, **19**, 4223.
26 R. A. Ewin, K. Jones and C. G. Newton, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1107.
27 Collect Data collection software, Nonius BV, Delft, The Netherlands, 1999.
28 Z. Otwinowski and W. Minor, *Processing of X-ray Diffraction Data Collected in Oscillation Mode*, in Methods in Enzymology, ed. C. W. Carter, Jr. and R. M. Sweet, Academic Press, New York, 1997, Volume 276 : Macromolecular Crystallography, part A, pp. 307–326.
29 G. M. Sheldrick, SHELXL-97, Program for refinement of crystal structures, University of Göttingen, Germany, 1997.
30 M. N. Burnett and C. K. Johnson, ORTEP-III: Oak Ridge Thermal Ellipsoid Plot Program for Crystal Structure Illustrations, Report ORNL-6895, Oak Ridge National Laboratory, Oak Ridge, TN, USA, 1996.
31 A. L. Spek, *Acta Crystallogr., Sect. A*, 1990, **46**, C34.
32 L. J. Barbour, X-SEED, A Graphical Interface to Shelx, University of Missouri, Columbia, MO 65211, USA, 1999.