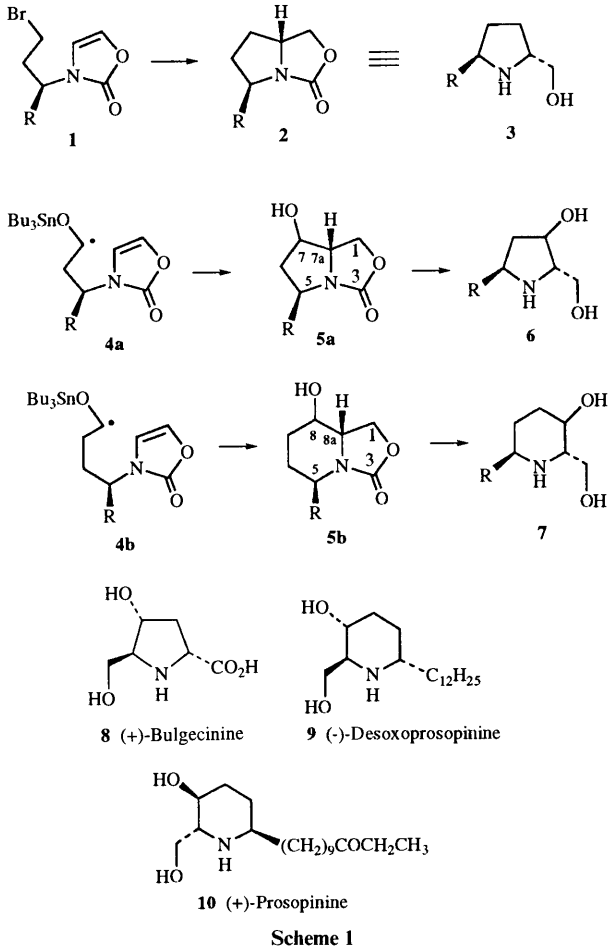
Diastereoselective synthesis of 2,5-disubstituted 3-hydroxypyrrolidine and 2,6-disubstituted 3-hydroxypiperidine derivatives by radical cyclisation; synthesis of (+)-bulgecinine and (−)-desoxoprosopinine

Yoko Yuasa, Jun Ando and Shiroshi Shibuya *

School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

Cyclisation of the *O*-stannyl ketyl, generated from the aldehyde 17 by reaction with tributyltin hydride in the presence of AIBN, gives the 5-benzyloxymethyl-7-hydroxypyrrolooxazolidin-2-ones as a diastereoisomeric mixture of 7α-ol 18 and 7β-ol 19 (2:1), with high diastereoselectivity with respect to the 5,7a positions. (+)-Bulgecinine 8 is enantioselectively synthesised by stereospecific reduction of the ketone 20, derived from compounds 18 and 19. In a similar way, cyclisation of compound 40 gives a 2:1 mixture of compounds 41 and 42. Conversion of compound 41 into (−)-desoxoprosopinine 9 is successfully achieved.

The development of new methodology for achieving stereocontrol in the construction of cyclic systems is of particular relevance to those containing pyrrolidine and piperidine rings in view of their rich stereochemical complexity which provides definitive structural features for a wide variety of natural products and biologically active compounds. In previous papers[1,2] from our laboratory, we reported that radical cyclisation using compound **1** resulted in predominant formation of 5-substituted 5,7a-*trans*-pyrrolooxazolidin-2-ones **2** with remarkably high diastereoselectivity. Cyclisation products **2** are known as synthetically equivalent forms of 5-substituted 2,5-*trans*-2-hydroxymethylpyrrolidines **3**, since the oxazolidinone ring can be easily cleaved to give the corresponding 2-amino alcohols. We are interested in establishing new methodology for the synthesis of 5-substituted 3-hydroxy-2-hydroxymethylpyrrolidines and 6-substituted 3-hydroxy-2-hydroxymethylpiperidines, which constitute the framework of an interesting group of pyrrolidine and piperidine alkaloids. In the last decade, generation of *O*-stannyl ketyls from aldehydes or ketones by treatment with tributyltin hydride in the presence of azoisobutyronitrile (AIBN) and subsequent cyclisation onto an unsaturated component has been developed for the synthesis of cycloalkanols.[3] In view of these papers, we have examined closely the cyclisation at the 4-position of the $\Delta^{4,5}$-oxazolidinones, by using the *O*-stannyl ketyls **4a**[4] and **4b**[5], to establish a facile and efficient method for a diastereoselective synthesis of 5-substituted 3-hydroxy-2-hydroxymethylpyrrolidines **6** and their piperidine analogues **7**. The reaction was found to proceed with remarkably high diastereoselectivity with regard to the relative configuration of 5/7a and 5/8a during the ring closure to compounds **5a** and **5b**, respectively, although the diastereoselectivity was not high with respect to the relative configuration of 7/7a (for **5a**) and 8/8a (for **5b**). The cyclisation was applied to a synthesis of our target compound (+)-bulgecinine **8**,[6] the enantiomer of natural (−)-bulgecinine[7] a constituent amino acid of the glycopeptide bulgecins found in the culture of broth of *Pseudomonas acidphila* and *Pseudomonas mesoacidphila* and (−)-desoxoprosopinine **9**,[8] a reduction product of naturally occurring prosopinine **10**[9] which has been isolated from *Prosopis africana* Taub. Here, we describe a full account of these experiments.



Scheme 1

Results and discussion

Enantioselective synthesis of 5-substituted 3-hydroxy-2-hydroxymethylpyrrolidine: enantioselective synthesis of (+)-bulgecinine

Initially we focussed our attention on the *O*-stannyl ketyl cyclisation at the double bond of 4,5-oxazolinone in order to synthesise (+)-bulgecinine **8**.[6] The aldehyde **17**, used as the precursor for the generation of the *O*-stannyl ketyl, was prepared by using the acetonide **11**,[10] derived from (*S*)-malic acid, as the starting material (see Scheme 2). Protection of the hydroxyl group of **11** with TBDPS (TBDPSCl, imidazole),

followed by ring cleavage of the acetonide with *p*-TsOH in methanol afforded the diol **12** (80.4%). The regioselective benzylation at the primary hydroxy group of **12** was carried out according to Veyrieres' method.[11] Thus, treatment of **12** with Bu_2SnO, followed by benzyl bromide in the presence of tetrabutylammonium bromide gave **13** (87.0%) as a single product. In order to introduce the oxazolidinone skeleton, the hydroxy group of **13** was coupled with oxazolidine-2,4-dione by a Mitsunobu reaction[12] to give the *N*-substituted oxazolidine-2,4-dione **14** (65%). Conversion of compound **14** into the oxazoline **15** was successfully achieved its reduction with $NaBH_4$, followed by treatment with methanesulfonyl chloride in the presence of triethylamine. Methanesulfonic acid was spontaneously eliminated from the 4-methanesulfonate by treatment with triethylamine at room temperature to give compound **15** (75.2%). The *tert*-butyldiphenylsilyl group of **15** was removed by treatment with tetrabutylammonium fluoride and the resulting alcohol **16** was safely converted into the aldehyde **17** (79%); this was a precursor for the *O*-stannyl ketyl, by Swern oxidation procedure. The reaction of **17** with tributyltin hydride in benzene in the presence of AIBN under reflux gave 5-benzyloxymethyl-7α-hydroxypyrrolooxazolidine **18** and the 7β-isomer **19** (2:1) (86%). A particularly noteworthy feature in this reaction was that virtually complete stereocontrol with respect to alkene facility was achieved but only *ca.* 2:1 diastereoselection with respect to the ketyl centre. Predominant formation of **18** can be accounted for by the ring closure occurring from the thermodynamically more stable transition state **A** rather than **B** (see Scheme 2). In order to obtain each of the 7-epimers pure, we examined the stereospecific reduction of the ketone **20**, obtained by Swern oxidation of a mixture of compounds **18** and **19**. Reduction of the ketone **20** with $NaBH_4$ afforded the 7β-ol **19**, $[\alpha]_D$ +21.3 (*c* 1.1, $CHCl_3$) (88%), without formation of **18**. In contrast, reduction of **20** with K-Selectride gave compound **18**, $[\alpha]_D$ +2.0 (*c* 0.4, $CHCl_3$) (89%). Each of the relative configurations of 7a-H/7-H and 7a-H/5-H of compound **19** were assigned as clearly *trans* by a study of 2D NMR (NOESY) spectra of **21**, obtained by silylation (TBSCl in 78% yield, $[\alpha]_D$ −8.4 (*c* 1.2, $CHCl_3$) (see Fig. 1), although they were not determined at the stage of compound **19**.

Compound **19** was converted into 3-hydroxy-2-hydroxymethylpyrrolidine-5-carboxylic acid **23** (see Scheme 3). The relative configurations of compound **23** at 7a-H/7-H and 7a-H/5-H are the same as those in our target molecule (+)-**8**. Catalytic hydrogenolysis of **21** with 10% Pd–C in MeOH afforded the alcohol **22** (93%), mp 84–86 °C, $[\alpha]_D$ −30.6 (*c* 0.7, $CHCl_3$). Oxidation of the alcohol **22** with $RuCl_3$–$NaIO_4$ yielded **23** (70%), mp 61–63 °C, $[\alpha]_D$ −4.1 (*c* 1.2, $CHCl_3$). The oxazolidinone ring was subsequently cleaved with 10% NaOH–EtOH (reflux). The reaction mixture was, after being washed with benzene to remove non-polar material, purified by ion exchange chromatography (Dowex 50, H^+ form) to afford (+)-bulgecinine **8** (75%), $[\alpha]_D$ +16.7 (*c* 0.42, H_2O), mp 187–192 °C. The spectral results indicated that the product was an enantiomer of natural (−)-bulgecinine {lit.,[7b] $[\alpha]_D$ −15.6 (*c* 0.53, H_2O), mp 188–192 °C}.

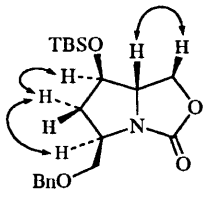
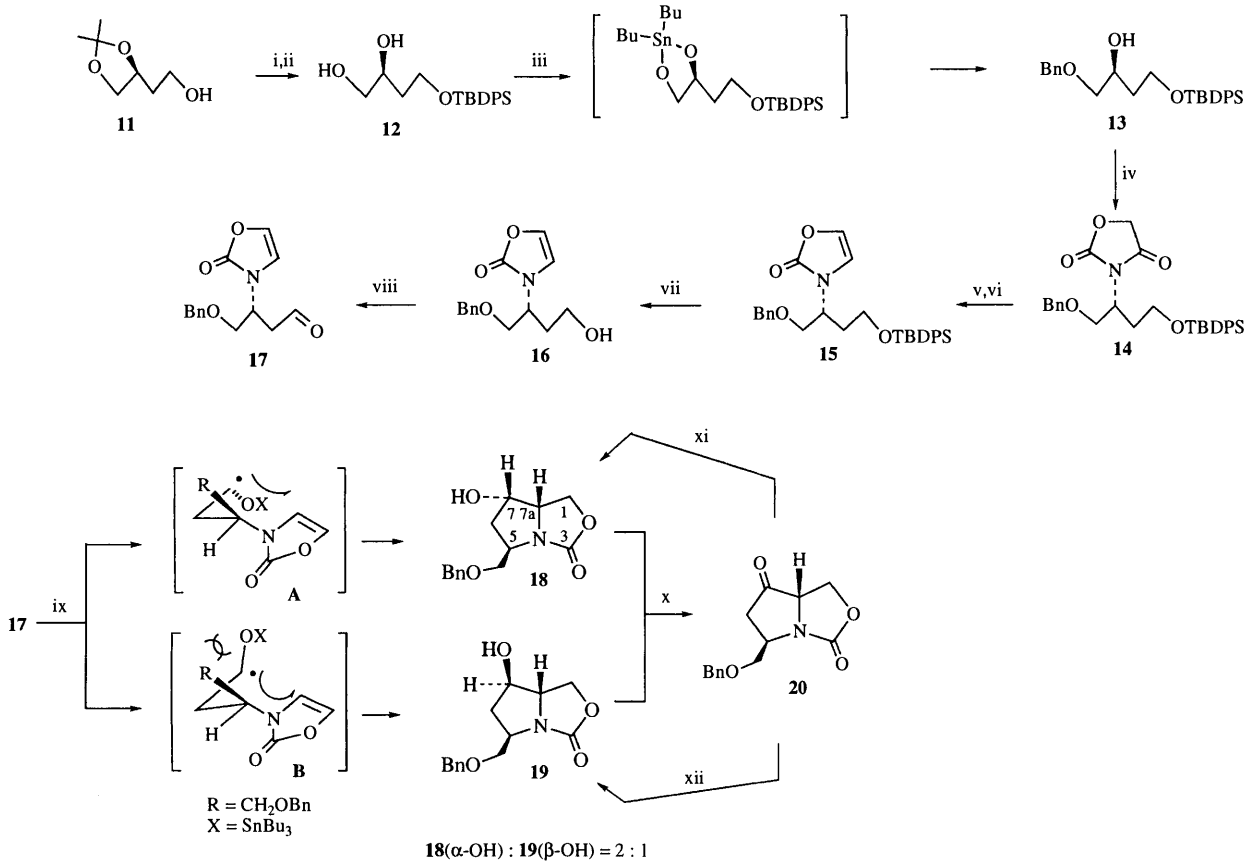
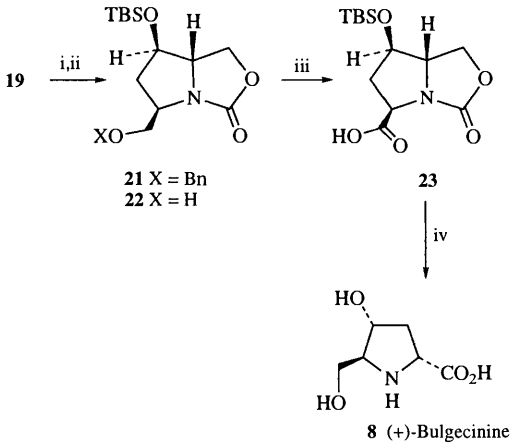


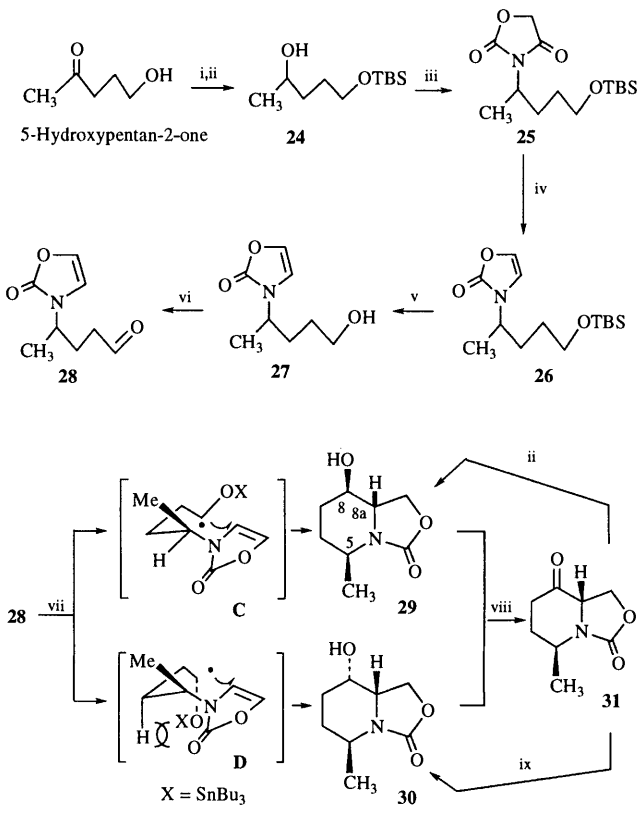
Fig. 1 NOESY correlations in **21**



Scheme 2 *Reagents and conditions:* i, TBSCl, imidazole, DMF; ii, *p*-TsOH, MeOH; iii, Bu_2SnO, toluene, and then BnBr, Bu_4NBr; iv, oxazolidine-2,4-dione, diisopropyl azodicarboxylate, Ph_3P; v, $NaBH_4$, MeOH; vi, CH_3SO_2Cl, Et_3N; vii, Bu_4NF, THF; viii, $(COCl)_2$, DMSO, Et_3N; ix, Bu_3SnH, AIBN, benzene, reflux, 5 h; x, $(COCl)_2$, DMSO, Et_3N; xi, K- or L-Selectride; xii, $NaBH_4$, MeOH



Scheme 3 *Reagents and conditions:* i, TBSCl, imidazole, DMF; ii, H_2, 10% Pd–C, MeOH; iii, $RuCl_3$–$NaIO_4$; iv, 10% NaOH–EtOH



Scheme 4 *Reagents and conditions:* i, TBSCl, imidazole, DMF; ii, $NaBH_4$, MeOH; iii, oxazolidine-2,4-dione, Ph_3P; iv, CH_3SO_2Cl, Et_3N; v, Bu_4NF, THF; vi, $(COCl)_2$, DMSO, Et_3N; vii, Bu_3SnH, AIBN, benzene; viii, PCC, CH_2Cl_2; ix, K- or L-Selectride

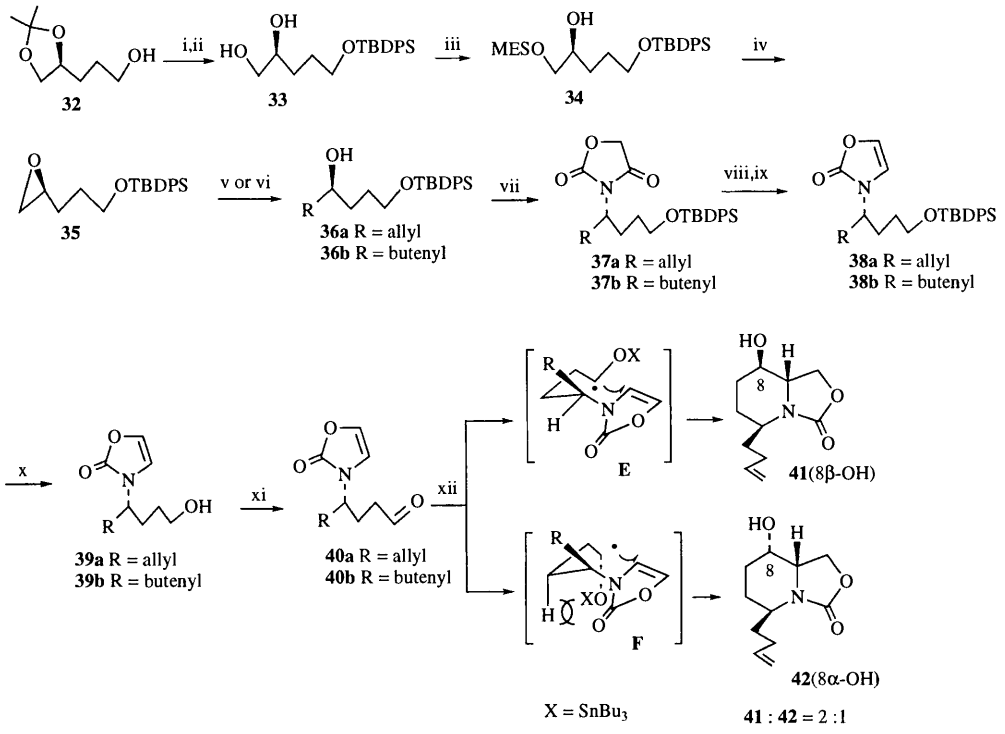
Synthesis of 6-substituted 3-hydroxy-2-hydroxymethylpiperidines

We studied in some depth whether the described method was applicable to a synthesis of 6-substituted 3-hydroxy-2-hydroxymethylpiperidines by using an homologous precursor, compound **28**. At first, we examined the synthesis of 5-methyl-8-hydroxyoxazolo[3,4-*a*]piperidine. The aldehyde **28** was prepared from 5-hydroxypentan-2-one (see Scheme 4). *O*-Protection of 5-hydroxypentan-2-one by treatment with TBSCl, followed by reduction of the resulting *O*-silylation product with $NaBH_4$ afforded the mono-protected pentane-1,4-diol **24**. Condensation of this with oxazolidine-2,4-dione under similar conditions to those employed for the formation of compound **14** yielded **25** (76%). Reduction of compound **25**, followed by treatment of the product with methanesulfonyl chloride in the presence of triethylamine gave the oxazolin-2-one **26** (73%), deprotection of which with tetrabutylammonium fluoride afforded the oxazolin-2-one **27** (81%). Conversion of **27** into the aldehyde **28** (72%), was safely achieved by Swern oxidation. Radical cyclisation of **28** was carried out by treatment with tributyltin hydride in the presence of AIBN in benzene, as for **17**, to give a 2:1 mixture of compounds **29** and **30** (85%). High *trans*-selectivity with respect 5-H/8a-H in both **29** and **30** can be accounted for in terms of reactions *via* transition states **C** or **D** to avoid $A^{1,3}$-strain between the methyl substituent and the amide carbonyl. In this reaction, the slight predominance of compound **29** may arise as a result of transition state **C** being more thermodynamically stable than **D**. Since a highly diastereoselective synthesis of each of **29** and **30** through stereospecific reduction of **31** had already been established,[13] a mixture of the two compounds was oxidised with pyridinium chlorochromate to yield compound **31** (86%), clearly identical with an authentic specimen[13] by comparison of the spectral data. Stereospecific reduction of compound **31** to yield both of 8α-ol and 8β-ol has already been reported.[13] Thus, new methodology for the highly diastereoselective synthesis of 6-substituted 3-hydroxy-2-hydroxymethylpiperidines was established.

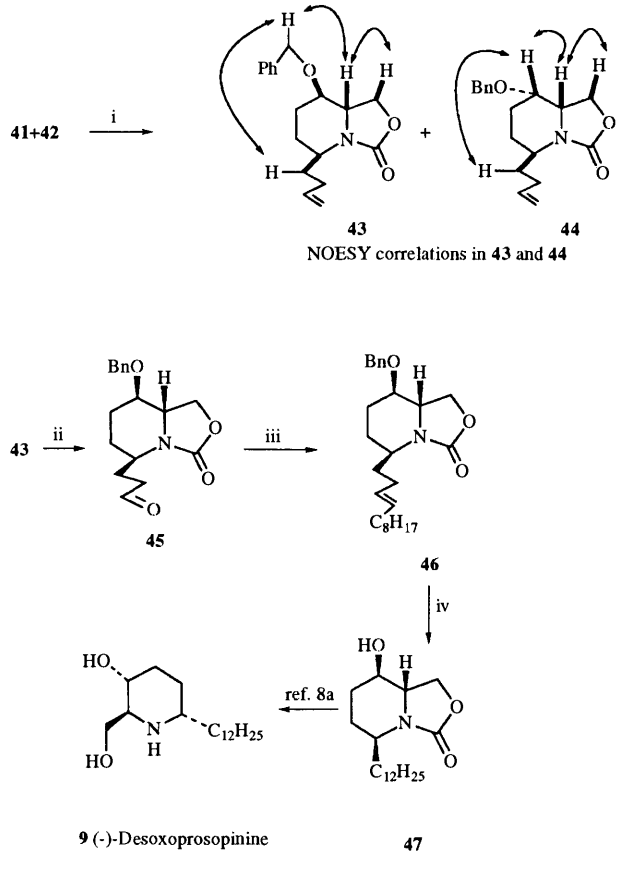
Synthesis of (−)-desoxoprosopinine

O-Stannyl ketyl cyclisation was then applied to the enantioselective synthesis of (−)-desoxoprosopinine **9**,[8] the reduction product of naturally occurring prosopinine **10**[9] which possesses a variety of antibiotic and anaesthetic properties.

The aldehydes **40a,b**, used as precursors for the *O*-stannyl ketyl, were synthesized from the acetonide **32**[14] by a similar method to that used in the preparation of compound **17** (see Scheme 5). Silylation of compound **32** with TBDPSCl and imidazole, followed by ring cleavage of the acetonide with *p*-TsOH in methanol afforded the diol **33** (76%). Regioselective mesitylenesulfonylation of **33** at the primary hydroxy group gave **34** (81%), which was treated with NaH in the presence of 18-crown-6 to afford the epoxide **35** (89%). The reaction of the epoxide **35** with vinyllithium,[15] prepared from vinylstannane and butyllithium, gave the alcohol **36a** (85%). The use of allylmagnesium bromide instead of vinyllithium afforded compound **36b** (85%). Condensation of compounds **36a,b** with oxazolidine-2,4-dione by a Mitsunobu reaction afforded compounds **37a** (78%) and **37b** (74%). Reduction of **37a,b** with $NaBH_4$ followed by treatment with methanesulfonyl chloride in the presence of triethylamine at room temperature gave the corresponding oxazolin-2-ones **38a** (71%) and **38b** (71%). Desilylation of **38a,b** with tetrabutylammonium fluoride, followed by Swern oxidation of the resulting alcohol **39a,b** afforded the aldehydes **40a** (79%) and **40b** (78%). The reaction of **40a** with tributyltin hydride in the presence of AIBN (benzene reflux) afforded a complex mixture of products including the desired cyclisation product. The unwanted reduction products were formed as a result of radical cyclisation at the terminal olefin by both *exo-trig* and *endo-trig* mechanisms. Attempts to isolate the desired cyclisation product failed, although the formation of a diastereoisomeric mixture of 8-hydroxyoxazolopiperidine was observed from ^1H NMR results. However, a similar reaction with compound **40b** yielded a diastereoisomeric mixture of the 8β-ol **41** and 8α-ol **42** (**41**/**42** = 2:1) (83%), key intermediates for a synthesis of prosopinine **10** and desoxoprosopinine **9**. In this reaction, the same phenomena, that is predominant formation of the 8,8a-*trans*-isomer *via* the transition state **E**, was observed as with compound **28**. Furthermore, as in the case of compound **28**, high *trans*-selectivity was also observed in respect of the relative configuration of 5-H/8a-H. Although separation of **41** and **42** from the reaction mixture was unsuccessful, each of *O*-benzyl derivatives **43** and **44**, obtained by benzylation of a mixture of compounds **41** and **42**, were obtained pure by column



Scheme 5 *Reagents and conditions:* i, TBSCl, imidazole, DMF; ii, *p*-TsOH, MeOH; iii, MESCl, pyridine; iv, NaH, 18-Crown-6, THF; v, vinyllithium, BF_3·Et_2O; vi, allylmagnesium bromide, CuI, THF; vii, oxazolidine-2,4-dione, diisopropyl azodicarboxylate, Ph_3P; viii, $NaBH_4$, MeOH; ix, CH_3SO_2Cl, Et_3N; x, Bu_4NF, THF; xi, $(COCl)_2$, DMSO, Et_3N; xii, Bu_3SnH, AIBN, benzene



Scheme 6 *Reagents and conditions:* i, NaH, BnBr, Bu_4NBr, THF; ii, O_3, MeOH–CH_2Cl_2 then Me_2S; iii, $C_9H_{19}Br$, Ph_3P, BuLi; iv, H_2, 10% Pd–C, MeOH–conc. HCl.

chromatography. Both relative configurations of 8a-H/8-H and 8a-H/5-H as *trans* for **43** were obtained (50%), $[\alpha]_D$ −49.9 (*c* 1.13, $CHCl_3$), by a study of their 2D NMR (NOESY). On the other hand, by this method the relative configurations of 8a-H/8-H was assigned as *cis* and 8a-H/5-H as *trans* for compound **43**, obtained in 25% yield, $[\alpha]_D$ +21.4 (*c* 1.17, $CHCl_3$). Ozonolysis of compound **43**, followed by condensation with nonylphosphonium bromide and BuLi afforded compound **46**, $[\alpha]_D$ −53.5 (*c* 0.89, $CHCl_3$) (88%). Hydrogenation of **46** (H_2/Pd–C) in methanol–conc. HCl (30 : 0.6) afforded compound **47**, mp 107–109 °C (lit.,[8b] 103–104 °C), $[\alpha]_D$ −19.4 (*c* 0.78, $CHCl_3$) (lit.,[8b] $[\alpha]_D^{24}$ −18.6 (*c* 0.44, $CHCl_3$). The spectral data for compound **47** were identical in all respects with those in the literature[8b] and those provided from Prof K. Tadano, Keio University. Since conversion of **47** into (−)-desoxoprosopinine has already been accomplished, this work constitutes a formal synthesis (−)-desoxoprosopinine **9**.

Experimental

General

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under nitrogen. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl and methylene dichloride (CH_2Cl_2) was distilled from CaH_2. All reactions were monitored by TLC using commercially available glass-backed plates. For column chromatography, silica gel 60 (0.043–0.063 mm) was used and the columns were eluted in the flash mode. ^1H NMR spectra were recorded on the Bruker AM400 or Varian Gemini 300 machines operating at 400 and 300 MHz, respectively, in $CDCl_3$. The chemical shift data for each signal is given in units of δ relative to tetramethylsilane (TMS) where δ (TMS) = 0. The multiplicity of the signal is indicated as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, br = broad signal. Coupling constants (*J*) are given in Hz. ^{13}C NMR spectra were recorded in $CDCl_3$ on the Bruker AM-400 (100 MHz). Chemical shifts are reported relative to $CDCl_3$ (central line of triplet, δ_C 77.0) unless stated otherwise. Optical rotations were determined with a JASCO DIP-4 polarimeter and IR spectra were recorded by using Perkin-Elmer 1710 spectrometer and only characteristic bands were given indicating representative

functional groups such as OH and C=O. Mass spectra (MS) were measured on a TSQ 700 and VG Auto Spec instrument.

(*S*)-4-*tert*-Butyldiphenylsilyloxybutane-1,2-diol 12

Triethylamine (26.0 g, 257 mmol) was slowly added to an ice-cooled mixture of compound **11** (25.0 g, 171 mmol), TBDPSCl (47.1 g, 171 mmol), 4-(dimethylamino)pyridine (2.09 g, 17.1 mmol) and CH_2Cl_2 (400 cm^3). After the reaction mixture had been stirred at the same temperature for 10 min, it was warmed to room temperature, stirred for 10 h and then poured onto water and extracted with $CHCl_3$. The extract was evaporated and the resulting residue was chromatographed on silica gel. Elution with hexane–ethyl acetate yielded the silylation product, which was dissolved in methanol (80 cm^3) and then treated with *p*-TsOH·H_2O (3.25 g, 17.1 mmol) at room temperature. The mixture was stirred for 0.5 h at the same temperature after which it was made basic with 5% aqueous $NaHCO_3$ and then evaporated. The resulting residue was diluted with water and extracted with $CHCl_3$. The extract was evaporated and the resulting residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (6:1) afforded compound **12** (47.4 g, 80.4%) as colourless needles, mp 72–74 °C; $[\alpha]_D$ +2.78 (*c* 1.87, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3408 (OH); δ_H($CDCl_3$) 1.05 (9 H, m), 1.60–1.72 (1 H, m), 1.75–1.88 (1 H, m), 3.54 (dd, *J* 5.8, 11.1), 3.68 (1 H, dd, *J* 7.1, 11.1), 3.90 (2 H, dd, *J* 4.9, 6.2), 3.98–4.07 (1 H, m), 7.38–7.50 (6 H, m) and 7.67–7.73 (4 H, m); *m*/*z* (EI), 327 (M^+ − Bu^t) (Found: C, 69.65; H, 8.2. $C_{20}H_{28}O_3Si$ requires C, 69.75; H, 8.2%).

(*S*)-1-Benzyloxy-4-*tert*-butyldiphenylsilyloxybutan-2-ol 13

A mixture of compound **12** (33.0 g, 95.8 mmol), Bu_2SnO (35.8 g, 144 mmol) and toluene (500 cm^3) was stirred and heated under reflux for 4 h in a Dean-Stark apparatus with removal of water. The mixture was then evaporated to 250 cm^3 and treated with benzyl bromide (49.2 g, 287 mmol) and tetrabutylammonium bromide (15.4 g, 47.9 mmol) at 80 °C whilst being stirred. Stirring was continued at the same temperature for 24 h after which the mixture was poured onto water and extracted with $CHCl_3$. The extract was evaporated and the resulting residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (20:1) yielded compound **13** (36.2 g, 87.0%) as a colourless oil, $[\alpha]_D$ −0.98 (*c* 1.43, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3461 (OH); δ_H($CDCl_3$) 1.05 (9 H, s), 1.70–1.84 (2 H, m), 3.43 (1 H, dd, *J* 6.8, 9.5), 3.51 (1 H, dd, *J* 4.2, 9.5), 3.79–3.87 (1 H, m), 4.08–4.13 (1 H, m), 4.56 (2 H, s), 7.26–7.49 (1 H, m), 7.65–7.72 (4 H, m); *m*/*z* (CI) 435 (M^+ + 1).

(*R*)-3-(1-Benzyloxy-4-*tert*-butyldiphenylsilyloxybutan-2-yl)-oxazolidine-2,4-dione 14

A solution of diisopropyl azodicarboxylate (1.71 g, 8.47 mol) in THF was added dropwise to a stirred and ice-cooled mixture of compound **13** (3.68 g, 8.47 mmol), oxazolidine-2,4-dione (0.85 g, 8.47 mmol), triphenylphosphine (2.22 g, 8.47 mmol) and THF (50 cm^3). After being stirred at the same temperature for 10 min, the mixture was kept at room temperature for 12 h with continued stirring. The mixture was evaporated to dryness and the residue chromatographed on silica gel. Elution with hexane–AcOEt (15:1) gave **14** (2.84 g, 64.8%), $[\alpha]_D$ −14.0 (*c* 1.00, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1819 (C=O) and 1740 (C=O); δ_H($CDCl_3$) 1.01 (9 H, s), 1.82–1.94 (1 H, m), 2.25–2.27 (1 H, m), 3.60 (1 H, dd, *J* 4.9, 10.1), 3.59–3.74 (2 H, m), 3.93 (1 H, dd, *J* 10.0, 10.1), 4.47 (1 H, dd, *J* 12.0), 4.48 (2 H, s), 4.57 (1 H, d, *J* 12.0), 4.58–4.70 (1 H, m), 7.27–7.48 (11 H, m) and 7.60–7.68 (4 H, m); *m*/*z* (EI) 460 (M^+ − Bu^t) [Found (HRMS): (M^+ − Bu^t), 460.1603. Calc. for $C_{26}H_{26}NO_5Si$: (*M* − Bu^t), 460.1580].

(*R*)-3-(1-Benzyloxy-4-*tert*-butyldiphenylsiloxybutan-2-yl)-2,3-dihydrooxazol-2-one 15

$NaBH_4$ (281 mg, 7.40 mmol) was added in small portions to a stirred and ice-cooled solution of **14** (2.55 g, 4.93 mmol) in methanol (20 cm^3). After being stirred at the same temperature for 0.5 h and then for a further 2 h at room temperature, the reaction mixture was quenched with acetone and evaporated. The resulting residue was diluted with water and extracted with $CHCl_3$. The extract was evaporated and the resulting residue was chromatographed on silica gel with hexane–ethyl acetate as eluent. After evaporation of the solvent, the resulting residue together with triethylamine (1.0 g, 9.86 mmol) was dissolved in CH_2Cl_2 (10 cm^3) and treated with CH_3SO_2Cl (0.85 g, 7.40 mmol) whilst the mixture was being stirred and cooled with ice. After continued stirring for 12 h at room temperature, the mixture was diluted with water and extracted with $CHCl_3$. The organic layer was washed with 0.5 mol dm^{-3} hydrochloric acid and 5% aqueous $NaHCO_3$ and then evaporated. The residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (8:1) yielded **15** (1.86 g, 75.2%); $[\alpha]_D$ +15.72 (*c* 0.92, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1748 (C=O); δ_H($CDCl_3$) 1.06 (9 H, s), 1.97–2.08 (2 H, m), 3.59–3.76 (4 H, m), 4.40–4.50 (1 H, m), 4.47 (1 H, d, *J* 11.8), 4.53 (1 H, d, *J* 11.8), 6.57 (1 H, d, *J* 2.0), 6.74 (1 H, d, *J* 2.0), 7.25–7.50 (11 H, m) and 7.61–7.72 (4 H, m); *m*/*z* (EI) 444 (M^+ − Bu^t) [Found (HRMS): (M^+ − Bu^t), 444.1630. Calc. for $C_{26}H_{26}NO_4Si$: (*M* − Bu^t), 444.1631].

(*R*)-3-(1-Benzyloxy-4-hydroxybutan-2-yl)-2,3-dihydrooxazol-2-one 16

A mixture of **15** (1.86 g, 3.71 mmol) and tetrabutylammonium fluoride (0.65 mol dm^{-3} THF solution; 11.4 cm^3) was stirred at room temperature for 1.5 h after which it was evaporated and the resulting residue chromatographed on silica gel. Elution with hexane–ethyl acetate (2:1) and then $CHCl_3$–methanol (9:1) gave **16** (928 mg, 95.1%) as a colourless oil; $[\alpha]_D$ +33.18 (*c* 1.31, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3403 (OH) and 1724 (C=O); δ_H($CDCl_3$) 1.90–1.97 (2 H, m), 3.46–3.54 (1 H, m), 3.65–3.73 (3 H, m), 4.38–4.44 (1 H, m), 4.53 (1 H, d, *J* 11.9), 4.59 (1 H, d, *J* 11.9), 6.79 (1 H, d, *J* 1.9), 6.81 (1 H, d, *J* 1.9) and 7.28–7.40 (5 H, m); *m*/*z* (EI) 263 (M^+) (Found: C, 63.2; N, 5.2; H, 6.45. $C_{14}H_{17}NO_4$ requires C, 63.9; N, 5.3; H, 6.5%).

(*R*)-3-(1-Benzyloxy-4-oxobutan-2-yl)-2,3-dihydrooxazol-2-one 17

DMSO (1.78 g, 22.8 mmol) was added to a stirred solution of oxalyl chloride (2.17 g, 17.1 mmol) in CH_2Cl_2 (130 cm^3) at −78 °C. After the mixture had been stirred for 15 min at the same temperature, a solution of **16** (3.0 g, 11.4 mmol) in CH_2Cl_2 (10 cm^3) was slowly added to it and stirring continued for 1 h at the same temperature. After this, triethylamine (5.20 g, 51.4 mmol) was added to the mixture and stirring continued at −78 °C for 1 h and then at room temperature for 1 h. The mixture was then poured onto water and extracted with $CHCl_3$. The extract was evaporated and the resulting residue was chromatographed on silica gel with hexane–ethyl acetate (2:1) as eluent to give **17** as a colourless oil (2.35 g, 78.9%); $[\alpha]_D$ +12.11 (*c* 1.35, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1746 (C=O); δ_H($CDCl_3$) 2.96 (1 H, dd, *J* 6.6, 18.1), 3.04 (1 H, dd, *J* 7.3, 18.1), 3.67 (1 H, dd, *J* 4.2, 9.9), 3.78 (1 H, dd, *J* 5.3, 9.9), 4.50 (1 H, d, *J* 6.7), 4.53 (1 H, d, *J* 6.7), 4.59–4.67 (1 H, m), 6.70 (1 H, d, *J* 2.1), 6.76 (1 H, d, *J* 2.1), 7.27–7.39 (5 H, m) and 9.74 (1 H, s); *m*/*z* (EI) 261 (M^+) [Found (HRMS): (M^+), 261.1004. Calc. for $C_{14}H_{15}NO_4Si$: *M*, 261.1001].

Radical cyclisation of the ketone 17

A benzene solution of tributylin hydride (2.01 g, 6.90 mmol) and AIBN (10 mg) were slowly added to a solution of compound **17** (1.20 g, 4.60 mmol) in benzene (700 cm^3). After the addition, the mixture was further refluxed for 5 h and then evaporated. The resulting residue was chromatographed on silica gel. After removal of non-polar material by elution with hexane, elution with hexane–ethyl acetate (1:2) then afforded, a mixture of compounds **18** and **19** (1.04 g, 86.0%) as an oil; this was used for the following reaction.

(5*R*,7a*R*)-5-Benzyloxymethyltetrahydropyrrolo[1,2-*c*]oxazole-3,7-dione 20

DMSO (1.40 g, 18.0 mmol) was added to a stirred solution of oxalyl chloride (1.71 g, 13.5 mmol) in CH_2Cl_2 (150 cm^3) at −78 °C. Stirring was continued for 15 min at the same temperature, after which a solution of **18** and **19** (2.36 g, 8.97 mmol) in CH_2Cl_2 (10 cm^3) was slowly added to the mixture. After stirring had been continued for 1 h at −78 °C triethylamine (4.09 g, 40.4 mmol) was added to the mixture which was then stirred for 1 h with ice cooling. After this the mixture was poured onto water and extracted with $CHCl_3$. The extract was evaporated and the resulting residue was chromatographed on silica gel, with hexane–ethyl acetate (4:1) as eluent to give **20** (1.85 g, 70.9%) as a colourless oil; $[\alpha]_D$ −84.6 (*c* 0.91, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1757 (C=O); δ_H($CDCl_3$) 2.50–2.59 (2 H, m), 3.58 (1 H, dd, *J* 2.8, 9.6), 3.84 (1 H, dd, *J* 2.8, 9.6), 4.16 (1 H, dd, *J* 3.9, 9.8), 4.32 (1 H, dd, *J* 3.9, 9.2), 4.49 (1 H, dd, *J* 9.2, 9.8), 4.50 (1 H, d, *J* 12.0), 4.54 (1 H, dd, *J* 3.4, 7.5), 4.58 (1 H, d, *J* 12.0) and 7.23–7.38 (5 H, m); δ_C($CDCl_3$) 39.1, 56.2, 61.5, 65.1, 72.8, 73.4, 127.4 (2 lines), 127.9, 128.5 (2 lines), 137.2, 161.7 and 212.7; *m*/*z* (CI) 262 (M^+ + 1) [Found (HRMS): (M^+), 261.1014. Calc. for $C_{14}H_{15}NO_4$: *M*, 261.1004].

(5*R*,7*S*,7a*R*)-5-Benzyloxymethyl-7-hydroxytetrahydropyrrolo-[1,2-*c*]oxazol-3-one 18

K-Selectride (THF 1 mol dm^{-3} solution; 0.76 cm^3) was added to a stirred solution of **20** (100 mg, 0.38 mmol) in THF (5 cm^3) at −78 °C. After stirring had been continued at the same temperature for 2 h, the reaction mixture was decomposed with 10% aqueous ammonia and extracted with CH_2Cl_2. The extract was evaporated and the resulting residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (1:1) gave **18** (82 mg, 82.7%) as colourless needles, mp 149–151 °C; $[\alpha]_D$ +2.0 (*c* 0.3, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1731 (C=O); δ_H($CDCl_3$) 2.15–2.20 (2 H, m), 3.55 (1 H, dd, *J* 4.0, 9.8), 3.63 (1 H, dd, *J* 4.5, 9.8), 3.92 (1 H, dt, 3.2, 8.4), 4.18–4.22 (1 H, m), 4.22–4.27 (1 H, m), 4.41 (1 H, dd, *J* 8.4, 8.9), 4.51 (1 H, dd, *J* 3.2, 8.9), 4.53 (1 H, d, *J* 12.0), 4.60 (1 H, d, *J* 12.0) and 7.25–7.39 (5 H, m); δ_C($CDCl_3$) 38.3, 56.3, 63.3, 64.2, 71.4, 71.9, 73.3, 127.7 (3 lines), 128.4 (2 lines), 138.1 and 162.5; *m*/*z* (CI) 264 (M^+ + 1) (Found: C, 63.65; H, 6.5; N, 5.3. $C_{14}H_{17}NO_4$ requires C, 63.85; H, 6.5; N, 5.3%).

(5*R*,7*R*,7a*R*)-5-Benzyloxymethyl-7-hydroxytetrahydropyrrolo-[1,2-*c*]oxazol-3-one 19

Small portions of $NaBH_4$ (182 mg, 4.80 mmol) were added to a stirred and ice-cooled solution of **20** (834 mg, 3.20 mmol) in methanol (20 cm^3). Stirring was continued at the same temperature for 0.5 h and then at room temperature for an additional 2 h. After the mixture had been quenched with acetone it was evaporated and the resulting residue was diluted with water and extracted with $CHCl_3$. The extract was evaporated and the resulting residue was chromatographed on silica gel with hexane–ethyl acetate (1:1) as eluent to give **19** (790 mg, 93.9%) as a colourless oil; $[\alpha]_D$ +21.27 (*c* 1.10, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1731 (C=O); δ_H($CDCl_3$) 1.87 (1 H, dt, *J* 4.7, 13.6), 2.39 (1 H, dt, *J* 8.2, 13.6), 3.59 (1 H, dd, *J* 3.5, 9.7), 3.70 (1 H, dd, *J* 3.5, 9.7), 3.88 (1 H, dt, 4.7, 8.5), 4.03–4.11 (1 H, m), 4.12–4.18 (1 H, m), 4.22 (1 H, dd, *J* 4.7, 9.3), 4.55 (1 H, d, *J* 11.8), 4.56 (1 H, dd, *J* 8.5, 9.3), 4.64 (1 H, d, *J* 11.8) and 7.33–7.41 (5 H, m); δ_C($CDCl_3$) 37.0, 56.9, 64.5, 67.0, 72.2, 73.6, 74.6, 127.7 (3 lines), 128.3 (2 lines), 137.4 and 161.5; *m*/*z* 264 (M^+ + 1) [Found (HRMS): (M^+), 263.1134. Calc. for $C_{14}H_{17}NO_4$: *M*, 263.1158].

(5*R*,7*R*,7a*R*)-5-Benzyloxymethyl-7-*tert*-butyldimethylsilyloxy-tetrahydropyrrolo[1,2-*c*]oxazol-3-one 21

A mixture of **19** (785 mg, 2.98 mmol), TBSCl (495 mg, 3.28 mmol), imidazole (223 mg, 3.28 mmol) and DMF (3.5 cm^3) was stirred at room temperature for 10 h and then poured onto water and extracted with ether. The extract was evaporated and the resulting residue was chromatographed on silica gel with hexane–ethyl acetate (10:1) as eluent to give **21** (876 mg, 78.0%) as a colourless oil; $[\alpha]_D$ −8.40 (*c* 1.02, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1762 (C=O); δ_H($CDCl_3$) 0.07 (6 H, s), 0.88 (9 H, s), 1.83 (1 H, dt, *J* 8.0, 12.8), 2.35 (1 H, dt, *J* 7.7, 12.8), 3.56 (2 H, d, *J* 5.0), 3.71 (1 H, dt, *J* 2.7, 7.8), 3.95 (1 H, q, *J* 8.0), 4.02–4.07 (1 H, m), 4.23 (1 H, dd, *J* 2.7, 9.2), 4.47 (1 H, dd, *J* 7.8, 9.2), 4.56 (1 H, d, *J* 12.1), 4.64 (1 H, d, *J* 12.1) and 7.30–7.36 (5 H, m); δ_C($CDCl_3$) −4.9, −4.7, 17.7 (3 lines), 25.5, 37.3, 56.5, 64.0, 66.1, 72.1, 73.0, 75.0, 127.5 (3 lines), 128.2 (2 lines), 137.9 and 161.2; *m*/*z* (CI) 378 (M^+ + 1) [Found (HRMS): 377.2016. Calc. for $C_{20}H_{31}NO_4Si$: *M*, 377.2022].

(5*R*,7*R*,7a*R*)-7-*tert*-Butyldimethylsilyloxy-5-hydroxymethyl-tetrahydropyrrolo[1,2-*c*]oxazol-3-one 22

A mixture of **21** (875 mg, 2.32 mmol), 10% Pd–C (12.5 mg) and methanol (25 cm^3) was shaken at room temperature under the atmosphere of hydrogen for 24 h after which it was filtered to remove the Pd–C and evaporated. The resulting residue was chromatographed on silica gel with hexane–ethyl acetate (3:1) as eluent to give **22** (597 mg, 89.6%) as colourless needles, mp 84–86 °C (hexane–ethyl acetate); $[\alpha]_D$ −30.6 (*c* 0.69, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1760 (C=O); δ_H($CDCl_3$) 0.07 (6 H, s), 0.88 (9 H, s), 1.73 (1 H, dt, *J* 8.9, 12.9), 2.35 (1 H, dt, *J* 7.4, 12.9), 3.58 (1 H, dd, *J* 5.2, 11.4), 3.70–3.82 (2 H, m), 3.90–4.05 (2 H, m), 4.26 (1 H, dd, *J* 3.5, 9.3) and 4.54 (1 H, dd, *J* 8.3, 9.3); δ_C($CDCl_3$) −4.8, −4.6, 17.9 (3 lines), 25.6, 37.0, 59.3, 64.0, 65.3, 67.0, 76.0 and 156.8; *m*/*z* (CI) 288 (M^+ + 1) (Found: C, 53.9; H, 8.65; N, 4.9. $C_{13}H_{25}NO_4Si$ requires C, 54.3; H, 8.75; N, 4.85%).

(5*R*,7*R*,7a*R*)-7-*tert*-Butyldimethylsilyloxy-5-carboxytetrahydro-pyrrolo[1,2-*c*]oxazol-3-one 23

A mixture of **22** (597 mg, 2.08 mmol), $NaIO_4$ (1.78 g, 8.33 mmol), $RuCl_3 \cdot 3H_2O$ (12 mg, 0.046 mmol), MeCN (4.2 cm^3), CCl_4 (4.2 cm^3) and H_2O (6.3 cm^3) was stirred at room temperature for 2 h and then extracted with CH_2Cl_2. The extract was evaporated and the resulting residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (1:1) gave **23** (438 mg, 69.9%) as colourless needles, mp 61–63 °C (hexane–ethyl acetate); $[\alpha]_D$ −4.05 (*c* 1.19, $CHCl_3$); δ_H($CDCl_3$) 0.08 (6 H, s), 0.90 (9 H, s), 2.07 (1 H, dt, *J* 9.3, 13.2), 2.67 (1 H, ddd, *J* 7.1, 8.8, 13.2), 3.86 (1 H, dt, *J* 3.0, 7.7), 4.01 (1 H, q, *J* 7.9), 4.27 (1 H, dd, *J* 3.0, 9.3), 4.50 (1 H, dd, *J* 8.0, 8.3) and 4.59 (1 H, dd, *J* 8.3, 9.5); δ_C($CDCl_3$) −4.8, −4.6, 17.9 (3 lines), 25.6, 38.7, 57.7, 64.3, 66.7, 74.7, 161.0 and 175.4 (Found: C, 51.6; H, 7.75; N, 4.55. $C_{13}H_{23}NO_5Si$ requires C, 51.8; H, 7.7; N, 4.65%).

(2*R*,4*R*,5*S*)-4-Hydroxy-5-hydroxymethylproline, (+)-bulgecinine 8

A mixture of **23** (415 mg, 1.38 mmol) and 10% aqueous NaOH and EtOH (1.5 cm^3) was heated under reflux for 24 h after which it was evaporated. The resulting residue was purified by ion exchange chromatography (Dowex 50W). With 2.5% aqueous ammonia as eluent to give **8** (97.5 mg, 44.0%) as colourless crystals, mp 187–192 °C (lit.,[7b] 188–192 °C), $[\alpha]_D$ +16.7 (*c* 0.42, H_2O) {lit.,[7b] $[\alpha]_D$ −15.6 (*c* 0.53, H_2O)}; the spectral data were identical with those in the literature.[7b]

5-*tert*-Butyldimethylsilyloxypentan-2-ol 24

A mixture of 5-hydroxypentan-2-one (4.59 g, 45.0 mmol), DMF (50 cm^3), TBSCl (6.78 g, 45.0 mmol) and imidazole (3.06 g, 45.0 mmol) was stirred at room temperature for 12 h after which it was poured onto water and extracted with ether. The extract was evaporated and the resulting residue was chromatographed on silica gel using hexane–ethyl acetate (10:1) as eluent. Evaporation of the eluate gave a colourless oil (8.65 g, 89.0%), a stirred solution of which (8.65 g) in methanol (250 cm^3) was treated with $NaBH_4$ (2.56 g, 67.5 mmol) whilst being cooled in

ice. After the mixture had been stirred at the same temperature for 0.5 h, it was further stirred at room temperature for 2 h and then quenched with acetone and evaporated. The resulting residue was diluted with water and extracted with $CHCl_3$. The extract was evaporated and the resulting residue was chromatographed on silica gel with hexane–ethyl acetate (8:1) as eluent to afford **24** as a colourless oil (7.66 g, 78.1 %); ν_{max}(neat)/cm^{-1} 3359 (OH); δ_H($CDCl_3$) 0.05 (6 H, s), 0.89 (9 H, s), 1.18 (3 H, d, *J* 6.2), 1.46–1.69 (4 H, m), 3.60–3.72 (2 H, m), 3.73–3.86 (1 H, m); *m*/*z* (EI) 161 (M^+ − Bu^t) [Found (HRMS): (M^+ − Bu^t) 161.0998. Calc. for $C_{11}H_{26}O_2Si$: (*M* − Bu^t), 161.0995].

3-(5-*tert*-Butyldimethylsilyloxypentan-2-yl)oxazolidine-2,4-dione 25

Compound **24** (7.65 g, 35.1 mmol) was allowed to react with oxazolidine-2,4-dione (3.72 g, 36.8 mmol), triphenylphosphine (9.65 g, 36.8 mmol) and diisopropyl azodicarboxylate (7.44 g, 36.8 mmol) and then worked up as in a preparation of compound **14**. The product was separated by column chromatography on silica gel with hexane–ethyl acetate (6:1) as eluent. Evaporation of the eluate gave **25** (7.92 g, 75.5%) as a colourless oil; ν_{max}(neat)/cm^{-1} 1820 (C=O) and 1741 (C=O); δ_H($CDCl_3$) 0.04 (6 H, s), 0.88 (9 H, s), 1.43 (3 H, d, *J* 7.0), 1.39–1.57 (2 H, m), 1.72–1.84 (1 H, m), 1.94–2.08 (1 H, m), 3.57–3.63 (2 H, m), 4.09–4.23 (1 H, m) and 4.62 (2 H, s); *m*/*z* (EI) 244 (M^+ − Bu^t) [Found (HRMS): (M^+ − Bu^t), 244.1005. Calc. for $C_{14}H_{27}NO_4Si$: (*M* − Bu^t), 244.1006].

3-(5-*tert*-Butyldimethylsilyloxypentan-2-yl)-2,3-dihydrooxazol-2-one 26

Compound **25** (8.13 g, 27.0 mmol) was reduced with $NaBH_4$ (1.54 g, 40.5 mmol) in methanol (150 cm^3) and worked up as in the preparation of compound **15**. The reduction product was treated with CH_3SO_2Cl (4.64 g, 40.5 mmol) and triethylamine (5.46 g, 54.0 mmol) and the reaction mixture worked up as in the preparation of compound **15**, the product being separated by column chromatography on silica gel with hexane–ethyl acetate (8:1) as eluent. Evaporation of the eluate gave compound **26** (5.32 g, 72.6%) as a colourless oil, ν_{max}(neat)/cm^{-1} 1747 (C=O); δ_H($CDCl_3$) 0.04 (6 H, s), 0.88 (9 H, s), 1.30 (3 H, d, *J* 6.8), 1.39–1.58 (2 H, m), 1.63–1.72 (2 H, m), 3.60 (2 H, m), 4.08–4.19 (1 H, m), 6.52 (1 H, d, *J* 2.1) and 6.80 (1 H, d, *J* 2.1); *m*/*z* (EI) 228 (M^+ − Bu^t) [Found (HRMS): (M^+ − Me), 270.1525. Calc. for $C_{13}H_{24}NO_3Si$: (*M* − Me), 270.1536].

3-(5-Hydroxypentan-2-yl)-2,3-dihydrooxazol-2-one 27

Compound **26** (5.32 g, 18.7 mmol) was treated with tetrabutylammonium fluoride (0.65 mol dm^{-3} THF solution; 57.4 cm^3) and worked up as in the preparation of compound **16**. The product was purified by column chromatography on silica gel with hexane–ethyl acetate (2:1) and then $CHCl_3$–methanol (9:1) as eluents to give **27** (2.59 g, 81.1%) as a colourless oil; ν_{max}(neat)/cm^{-1} 3418 (OH) and 1736 (C=O); δ_H($CDCl_3$) 1.32 (3 H, d, *J* 6.8), 1.65–1.79 (4 H, m), 3.67 (2 H, dt, *J* 2.1, 6.1), 4.13–4.22 (1 H, m), 6.54 (1 H, d, *J* 2.1) and 6.81 (1 H, d, *J* 2.1); *m*/*z* (EI), 171 (M^+) [Found (HRMS): M^+, 171.0893. Calc. for $C_8H_{13}NO_3$: *M*, 171.0895].

3-(5-Oxopentan-2-yl)-2,3-dihydrooxazol-2-one 28. Compound **27** (2.60 g, 15.2 mmol) was treated with oxalyl chloride (2.90 g, 22.8 mmol) and DMSO (2.37 g, 30.4 mmol) and worked up as in the preparation of compound **17**. The product was separated by column chromatography on silica gel with hexane–ethyl acetate (2:1) as eluent to give compound **28** (1.86 g, 72.4%) as a colourless oil; ν_{max}(neat)/cm^{-1} 1741 (C=O); δ_H($CDCl_3$) 1.34 (3 H, d, *J* 6.8), 1.84–2.03 (2 H, m), 2.40–2.61 (2 H, m), 4.08–4.19 (1 H, m), 6.52 (1 H, d, *J* 2.0), 6.82 (1 H, d, *J* 2.0) and 9.76 (1 H, s); *m*/*z* 169 (M^+) [Found (HRMS): M^+, 169.0721. Calc. for $C_8H_{11}NO_3$: *M*, 169.0739].

Radical cyclisation of compound 28

A solution of compound **28** (1.20 g, 7.10 mmol) in benzene (500 cm^3) was treated with tributyltin hydride (2.48 g, 8.53 mmol) and AIBN (15 mg) and the mixture worked up as in the radical cyclisation of compound **17**. The product was purified by column chromatography on silica gel with hexane–ethyl acetate (3:1) as eluent to give a mixture of **29** and **30** (1.03 g, 84.7%); this was used for the following reaction.

5-Methyloxazolo[3,4-*a*]pyridine-3,8-dione 31

A mixture of compounds **29** and **30** (192 mg, 1.12 mmol) was added to a stirred solution of pyridinium chlorochromate (394 mg, 168 mmol) in CH_2Cl_2 (40 cm^3) at room temperature. Stirring was continued for 3 h, after which the mixture was diluted with ether and filtered to remove insoluble material. The filtrate was evaporated and the resulting residue was chromatographed on silica gel, with hexane–ethyl acetate (3:1) as eluent to afford compound **31** (163 mg, 86.3%), which was identical in all respects with an authentic sample.[13]

(*S*)-5-*tert*-Butyldiphenylsilyloxypentane-1,2-diol 33

Triethylamine (18.9 g, 187.5 mmol) was added dropwise to a stirred, ice-cooled mixture of compound **32** (20 g, 125 mmol), TBDPSCl (34.2 g, 125 mmol), 4-(dimethylamino)pyridine (1.53 g, 12.5 mmol) and CH_2Cl_2 (300 cm^3). After completion of the reaction, work-up as in a preparation of **12** gave a residue which was chromatographed on silica gel with hexane–ethyl acetate (20:1) as eluent to afford a colourless oil (46.0 g, 92.3%). This was treated with methanol (400 cm^3) in the presence of *p*-TsOH·H_2O (2.38 g, 12.5 mmol) after which the mixture was neutralised with 5% aqueous $NaHCO_3$ and evaporated. The residue was extracted with $CHCl_3$. The extract was evaporated and the resulting residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (6:1) afforded compound **33** (24.2 g, 76.3%); $[\alpha]_D$ −1.27 (*c* 1.73, $CHCl_3$); ν(neat)/cm^{-1} 3370 (OH); δ_H($CDCl_3$) 1.05 (9 H, s), 1.66–1.78 (4 H, m), 3.42–3.52 (1 H, m), 3.59–3.80 (2 H, m), 3.70 (2 H, m), 7.35–7.48 (6 H, m) and 7.65–7.72 (4 H, m); *m*/*z* (CI) 359 (M^+ + 1).

(*S*)-5-*tert*-Butyldiphenylsilyloxy-1-(2′,4′,6′-trimethylphenylsulfonyl)pentan-2-ol 34

2,4,6-Benzenesulfonyl chloride (13.45 g, 61.50 mmol) was added in three portions to a stirred solution of compound **33** (21.0 g, 58.6 mmol) in pyridine (250 cm^3) at −50 °C. The mixture was then warmed to room temperature, stirred for 48 h and then evaporated. The resulting residue was extracted with ethyl acetate and the extract evaporated. The residue was chromatographed on silica gel with hexane–ethyl acetate (10:1) as eluent to give compound **34** (25.7 g, 81.2%); $[\alpha]_D$ +1.97 (*c* 1.22, $CHCl_3$); δ_H($CDCl_3$) 1.03 (9 H, s), 1.61–1.73 (4 H, m), 2.31 (3 H, s), 2.64 (6 H, s), 3.66 (2 H, dd, *J* 5.0, 5.3), 3.84–3.99 (3 H, m), 6.98 (2 H, m), 7.34–7.47 (6 H, m) and 7.62–7.67 (4 H, m).

(*S*)-5-*tert*-Butyldiphenylsilyloxy-1,2-epoxypentane 35

A solution of compound **34** (25.0 g, 46.2 mmol) in THF (50 cm^3) and 18-crown-6 (1.22 g, 4.62 mmol) were added to an ice-cooled stirred suspension of 60% NaH (2.40 g, 60.11 mmol; used after removal of oil by washing with light petroleum) *in THF* (40 cm^3). The mixture was stirred at the same temperature for 10 min and then an additional 2 h at room temperature. After this, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution to the mixture which was then extracted with CH_2Cl_2. The extract was evaporated and the resulting residue was chromatographed on silica gel with hexane–ethyl acetate (10:1) as eluent to give compound **35** (14.0 g, 89.3%); $[\alpha]_D$ −3.41 (*c* 1.12, $CHCl_3$); δ_H($CDCl_3$) 1.06 (9 H, s), 1.61–1.79 (4 H, m), 2.47 (1 H, dd, *J* 2.7, 5.1), 2.74 (1 H, dd, *J* 4.1, 5.1), 2.92–2.95 (1 H, m), 3.72 (1 H, dt, *J* 1.6, 5.8), 7.36–7.50 (6 H, m) and 7.65–7.73 (4 H, m); *m*/*z* (EI) 383 (M^+ − Bu^t) [Found

(HRMS): (M^+ – Bu^t), 283.1152. Calc. for $C_{17}H_{19}O_2Si$: (M – Bu^t), 283.1154].

(*R*)-1-*tert*-Butyldiphenylsilyloxyhept-6-en-4-ol 36a

Vinyllithium (52.7 cm^3, 0.78 mmol in ether) and BF_3·Et_2O (5.84 g, 41.1 mmol) were added to a solution of compound **35** (3.50 g, 10.28 mmol) in THF (30 cm^3) cooled to −78 °C. The solution was stirred at −78 °C for 40 min and then quenched with methanol (30 cm^3) and 15% aqueous NaOH (10 cm^3). The organic solvent was removed by evaporation and the resulting residue was extracted with $CHCl_3$. The extract was evaporated and the resulting residue was chromatographed on silica gel with hexane–ethyl acetate (10:1) as eluent to give compound **36a** (3.21 g, 84.7%) as a colourless oil; $[\alpha]_D$ −2.68 (*c* 1.19, $CHCl_3$); ν_{max}(neat)/cm ^{1} 3418 (OH) and 1641 (C=C); δ_H($CDCl_3$) 1.04 (9 H, s), 1.62–1.75 (6 H, m), 1.62–1.75 (4 H, m), 2.17–2.32 (2 H, m), 3.64–3.72 (3 H, m), 5.10–5.17 (2 H, m), 5.77–5.91 (1 H, m) and 7.33–7.69 (10 H, m); *m*/*z* (EI) 311 (M^+ – Bu^t) [Found (HRMS): (M^+ – Bu^t) 311.1472. Calc. for $C_{19}H_{23}O_2Si$: (M – Bu^t) and 311.1467].

(*R*)-1-*tert*-Butyldiphenylsilyloxyoct-7-en-4-ol 36b

A solution of allylmagnesium bromide (1 mol dm^{-3}; 65.8 cm^3) was added to a stirred suspension of CuI (1.17 g, 6.17 mmol) in THF (200 cm^3) at −30 °C. Stirring was continued at the same temperature for 5 min after which a solution of compound **35** (14 g, 41.1 mmol) in THF (80 cm^3) was added to the mixture during 15 min. The mixture was then stirred for 2 h at room temperature after which it was quenched with 5% aqueous $NaHCO_3$ and extracted with ether. The extract was evaporated and the resulting residue was chromatographed on silica gel with hexane–ethyl acetate (8:1) as eluent to yield compound **36b** (13.3 g, 84.8%); $[\alpha]_D$ −2.39 (*c* 1.17, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3398 (OH) and 1641 (C=C); δ_H($CDCl_3$) 1.06 (9 H, s), 1.52–1.75 (6 H, m), 2.07–2.30 (2 H, m), 3.60–3.75 (1 H, m), 3.70 (2 H, dd, *J* 5.7, 5.8), 4.96–5.12 (2 H, m), 5.79–5.93 (1 H, m), 7.35–7.50 (6 H, m) and 7.65–7.74 (4 H, m); *m*/*z* (EI) 325 (M^+ – Bu^t) [Found (HRMS): (M^+ – Bu^t) 325.1632. Calc. for $C_{20}H_{25}O_2Si$: (M – Bu^t), 325.1624].

(*S*)-3-(1-*tert*-Butyldiphenylsilyloxyhept-6-en-4-yl)oxazolidine-2,4-dione 37a

Compound **36a** (12.9 g, 34.9 mmol) was treated with oxazolidine-2,4-dione (3.70 g, 36.6 mmol), triphenylphosphine (9.60 g, 36.6 mmol) and diisopropyl azodicarboxylate (7.39 g, 36.6 mmol) and the mixture worked up as in the preparation of compound **14**. The product was purified by column chromatography on silica gel with hexane–ethyl acetate (15:1) as eluent to give compound **37a** (12.3 g, 77.9%) as a colourless oil; $[\alpha]_D$ +6.01 (*c* 1.13, $CHCl_3$); ν_{max}/cm^{-1} 1818 (C=O), 1741 (C=O) and 1643 (C=C); δ_H($CDCl_3$) 1.04 (9 H, s), 1.48–1.58 (2 H, m), 1.79–1.90 (1 H, m), 2.01–2.11 (1 H, m), 2.39–2.47 (1 H, m), 2.67–2.78 (1 H, m), 3.62–3.69 (2 H, m), 4.04–4.11 (1 H, m), 4.58 (2 H, s), 5.05–5.12 (2 H, m), 5.61–5.72 (1 H, m) and 7.39–7.68 (10 H, m); *m*/*z* (EI) 394 (M^+ – Bu^t) [Found (HRMS): (M^+ – Bu^t), 394.1491. Calc. for $C_{22}H_{24}NO_4Si$: (M – Bu^t), 394.1475].

(*S*)-3-(1-*tert*-Butyldiphenylsilyloxyoct-7-en-4-yl)oxazolidine-2,4-dione 37b

Compound **36b** (13.3 g, 34.8 mmol) was treated with oxazolidine-2,4-dione (3.69 g, 36.5 mmol), triphenylphosphine (9.58 g, 36.5 mmol) and diisopropyl azodicarboxylate (7.39 g, 36.5 mmol) and the mixture worked up as in the preparation of compound **14**. The product was purified by column chromatography on silica gel with hexane–ethyl acetate (15:1) as eluent to give compound **37b** (12.0 g, 74.1%) as a colourless oil; $[\alpha]_D$ +2.85 (*c* 1.05, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1818 (C=O), 1741 (C=O) and 1642 (C=C); δ_H($CDCl_3$) 1.04 (9 H, s), 1.45–1.58 (2 H, m), 1.74–1.86 (2 H, m), 1.97–2.18 (4 H, m), 3.62–3.65 (2 H, m), 3.96–4.04 (1 H, m), 4.58 (2 H, s), 4.96–5.04 (2 H, m), 5.71–5.81 (1 H, m) and 7.31–7.71 (10 H, m); *m*/*z* (EI) 408 (M^+ – Bu^t) [Found (HRMS): (M^+ – Bu^t), 408.1630. Calc. for $C_{23}H_{26}NO_4Si$: (M – Bu^t), 408.1631].

(*S*)-3-(1-*tert*-Butyldiphenylsilyloxyhept-6-en-4-yl)-2,3-dihydro-oxazol-2-one 38a

Compound **37a** (12.3 g, 27.2 mmol) was reduced with $NaBH_4$ (1.55 g, 40.8 mmol) in methanol (150 cm^3) and worked up as in the preparation of compound **15**. The reduction product was treated with CH_3SO_2Cl (4.67 g, 40.8 mmol) and triethylamine (5.50 g, 54.8 mmol) and the reaction mixture worked up as in the preparation of compound **15**. The product was purified by column chromatography on silica gel with hexane–ethyl acetate (8:1) as eluent to give compound **38a** (8.34 g, 70.5%) as a colourless oil; $[\alpha]_D$ +9.09 (*c* 1.50, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1747 (C=O) and 1643 (C=C); δ_H($CDCl_3$) 1.04 (9 H, s), 1.48–1.88 (4 H, m), 2.30–2.41 (2 H, m), 3.63–3.74 (2 H, m), 4.01–4.06 (1 H, m), 5.04–5.09 (2 H, m), 5.66–5.75 (1 H, m), 6.45 (1 H, d, *J* 2.0), 6.77 (1 H, d, *J* 2.0) and 7.33–7.66 (10 H, m); *m*/*z* (EI) 378 (M^+ – Bu^t) [Found (HRMS): (M^+ – Bu^t), 378.1520. Calc. for $C_{22}H_{24}NO_3Si$: (M – Bu^t), 378.1525].

(*S*)-3-(1-*tert*-Butyldiphenylsilyloxyoct-7-en-4-yl)oxazolin-2-one 38b

Compound **37b** (11.4 g, 24.4 mmol) was reduced with $NaBH_4$ (1.39 g, 36.6 mmol) in methanol (150 cm^3) and the reaction mixture worked up as in the preparation of compound **15**. The reduction product was treated with CH_3SO_2Cl (4.19 g, 36.6 mmol) and triethylamine (4.93 g, 48.8 mmol) and the mixture worked up as in the preparation of compound **15**. The product was purified by column chromatography on silica gel with hexane–ethyl acetate (8:1) as eluent to give compound **38b** (7.82 g, 71.4%) as a colourless oil; $[\alpha]_D$ +2.68 (*c* 1.12, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1747 (C=O) and 1642 (C=C); δ_H($CDCl_3$) 1.04 (9 H, s), 1.49–1.81 (6 H, m), 1.98–2.06 (2 H, m), 3.62–3.70 (2 H, m), 3.93–3.98 (1 H, m), 4.97–5.06 (2 H, m), 5.70–5.81 (1 H, m), 6.44 (1 H, d, *J* 2.0), 6.80 (1 H, d, *J* 2.0) and 7.32–7.66 (10 H, m); *m*/*z* (EI) 392 (M^+ – Bu^t) [Found (HRMS): (M^+ – Bu^t), 392.1695. Calc. for $C_{23}H_{26}NO_3Si$: (M – Bu^t), 392.1682].

(*S*)-3-(1-Hydroxyhept-6-en-4-yl)-2,3-dihydrooxazol-2-one 39a

Compound **38a** (8.12 g, 18.7 mmol) was treated with tetrabutylammonium fluoride (0.65 mol dm^{-3} THF solution; 43.0 cm^3) and the mixture worked up as in the preparation of compound **16**. The product was purified by column chromatography on silica gel with hexane–ethyl acetate (2:1) and then $CHCl_3$–methanol (9:1) as eluents to give compound **39a** (2.83 g, 77.0%) as colourless oil; $[\alpha]_D$ +21.3 (*c* 1.50, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3425 (OH), 1736 (C=O) and 1643 (C=C); δ_H($CDCl_3$) 1.72–1.82 (2 H, m), 1.83–2.12 (2 H, m), 2.53–2.75 (2 H, m), 3.81–3.99 (2 H, m), 4.29–4.40 (1 H, m), 5.28–5.37 (2 H, m), 5.88–6.02 (1 H, m), 6.78 (1 H, d, *J* 2.0) and 7.05 (1 H, d, *J* 2.0); *m*/*z* (EI) 197 (M^+) [Found (HRMS): M^+, 197.1068. Calc. for $C_{10}H_{15}NO_3$: *M*, 197.1052].

(*S*)-3-(1-Hydroxyoct-7-en-4-yl)-2,3-dihydrooxazol-2-one 39b

Compound **38b** (8.09 g, 18.0 mmol) was treated with tetrabutylammonium fluoride (0.65 mol dm^{-3} THF solution; 41.5 cm^3) and the mixture worked up as in the preparation of compound **16**. The product was purified by column chromatography on silica gel with hexane–ethyl acetate (2:1) and then $CHCl_3$–methanol (9:1) as eluents to give compound **39b** (3.69 g, 97.2%) as colourless oil; $[\alpha]_D$ +9.73 (*c* 1.32, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3431 (OH), 1741 (C=O) and 1642 (C=C); δ_H($CDCl_3$) 1.46–2.05 (8 H, m), 3.60–3.64 (2 H, m), 3.96–4.05 (1 H, m), 4.95–5.03 (2 H, m), 5.67–5.80 (1 H, m), 6.50 (1 H, d, *J* 2.0) and 6.81 (1 H, d, *J* 2.0); *m*/*z* (EI) 211 (M^+) [Found (HRMS): M^+, 211.1202. Calc. for $C_{11}H_{17}NO_3$: *M*, 211.1208].

(*S*)-3-(1-Oxohept-6-en-4-yl)-2,3-dihydrooxazol-2-one 40a

Compound **39a** (3.0 g, 15.2 mmol) was treated with oxalyl

chloride (2.89 g, 22.8 mmol) and DMSO (2.38 g, 30.5 mmol) and the mixture worked up as in the preparation of compound **17**. The product was purified by column chromatography on silica gel with hexane–ethyl acetate (3:1) as eluent to give compound **40a** (2.35 g, 79.1%) as colourless oil; $[\alpha]_D$ +11.1 (*c* 1.38, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1747 (C=O) and 1643 (C=C); δ_H($CDCl_3$) 1.82–1.92 (1 H, m), 1.97–2.09 (1 H, m), 2.30–2.58 (4 H, m), 3.96–4.06 (1 H, m), 4.99–5.11 (2 H, m), 5.60–5.74 (1 H, m), 6.48 (1 H, d, *J* 2.0), 6.78 (1 H, d, *J* 2.0) and 9.72 (1 H, s); δ_C($CDCl_3$) 25.5, 38.4, 40.1, 53.5, 112.6, 118.7, 127.9, 132.7, 155.6 and 200.4; *m/z* (EI) 195 (M^+) [Found (HRMS): M^+, 195.0891. Calc. for $C_{10}H_{13}NO_3$: *M*, 195.0895].

(*S*)-3-(1-Oxooct-7-en-4-yl)-2,3-dihydrooxazol-2-one 40b

Compound **39b** (3.21 g, 15.2 mmol) was treated with oxalyl chloride (2.89 g, 22.8 mmol) and DMSO (2.38 g, 30.5 mmol) and the mixture worked up as in the preparation of compound **17**. The product was purified by column chromatography on silica gel with hexane–ethyl acetate (3:1) as eluent to give compound **40b** (2.47 g, 77.5%) as colourless oil; $[\alpha]_D$ +9.62 (*c* 1.26, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1746 (C=O) and 1642 (C=C); δ_H($CDCl_3$) 1.70–2.06 (6 H, m), 2.43–2.56 (2 H, m), 3.91–4.00 (1 H, m), 4.96–5.04 (2 H, m), 5.66–5.80 (1 H, m), 6.48 (1 H, d, *J* 2.0), 6.82 (1 H, d, *J* 2.0) and 9.73 (1 H, s); δ_C($CDCl_3$) 26.1, 29.9, 33.2, 40.0, 53.5, 110.9, 115.6, 128.1, 136.4, 155.5 and 200.4; *m/z* (EI) 209 (M^+) [Found (HRMS): M^+, 209.1072. Calc. for $C_{11}H_{15}NO_3$: *M*, 209.1052].

Radical cyclisation of the ketone 40b; synthesis of compounds 41 and 42

A solution of compound **40b** (1.48 g, 7.08 mmol) in benzene (500 cm^3) and tributyltin hydride (2.48 g, 8.53 mmol) was heated and worked up as for the radical cyclisation of compound **17**. The product was purified by column chromatography on silica gel with hexane–ethyl acetate (3:1) as eluent to give a mixture of compounds **41** and **42** (1.24 g, 83.0%); this was used for the following reaction.

***O*-Benzylation of a mixture of compounds 41 and 42**

A mixture of compounds **41** and **42** (1.50 g, 7.11 mmol) in dissolved THF (15 cm^3) was added to a stirred and ice-cooled suspension of 60% NaH (569 mg, 14.2 mmol; used after removal of oil by washing with light petroleum) in DMF (8 cm^3). Stirring was continued for 15 min at the same temperature after which benzyl bromide (2.43 g, 14.2 mmol) and tetrabutylammonium bromide (451.3 mg, 1.42 mmol) were added to the mixture. The mixture was stirred for 1 h with continued ice cooling and then for 12 h at room temperature; it was then poured onto ice–water and extracted with $CHCl_3$. The extract was evaporated and the resulting residue was chromatographed on silica gel with hexane–ethyl acetate (7:1) as eluent to give compound **43** (1.07 g, 49.9%) as a colourless oil; $[\alpha]_D$ −49.9 (*c* 1.13, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1752 (C=O) and 1641 (C=C); δ_H($CDCl_3$) 1.50–1.91 (6 H, m), 2.05–2.20 (2 H, m), 3.23 (1 H, ddd, *J* 4.3, 6.4, 9.3), 3.58 (1 H, ddd, *J* 4.6, 8.4, 9.3), 3.90–4.00 (1 H, m), 4.07 (1 H, dd, *J* 4.6, 8.9), 4.38 (1 H, dd, *J* 8.4, 8.9), 4.43 (1 H, d, *J* 11.6), 4.68 (1 H, d, *J* 11.6), 4.97–5.12 (2 H, m), 5.77–5.90 (1 H, m) and 7.25–7.41 (5 H, m); δ_C($CDCl_3$) 24.2, 26.4, 29.1, 30.3, 48.5, 54.3, 66.4, 70.5, 77.3, 115.1, 127.8 (2 lines), 127.9, 128.4 (2 lines), 137.3, 137.5 and 156.9; *m/z* (EI), 301 (M^+) and 246 (M^+ − CH_2=$CHCH_2CH_2$) [Found (HRMS): M^+, 301.1701. Calc. for $C_{18}H_{23}NO_3$: *M*, 301.1678]. Further elution with hexane–ethyl acetate (6:1) gave compound **44** (534 mg, 25.0%) as a colourless oil; $[\alpha]_D$ +21.4 (*c* 1.17, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1747 (C=O) and 1641 (C=C); δ_H($CDCl_3$) 1.48–1.88 (6 H, m), 2.04–2.20 (2 H, m), 3.43 (1 H, br s), 3.82 (1 H, ddd, *J* 2.4, 4.8, 8.8), 3.96–4.05 (1 H, m,), 4.22 (1 H, dd, *J* 8.2, 8.8), 4.32 (1 H, dd, *J* 4.8, 8.2), 4.40 (1 H, d, *J* 12.2), 4.69 (1 H, d, *J* 12.2), 4.95–5.12 (2 H, m), 5.78–5.91 (1 H, m) and 7.25–7.43 (5 H, m); δ_C($CDCl_3$) 20.7, 21.1, 29.3, 30.4, 48.6, 53.7, 63.5, 70.0, 70.6, 114.9, 127.2 (2 lines), 127.5, 128.3 (2 lines), 137.6, 137.8 and 157.5; *m/z* (EI), 301 (M^+), 246 (M^+ − CH_2=$CHCH_2CH_2$) [Found (HRMS): M^+, 301.1672. Calc. for $C_{18}H_{23}NO_3$: *M*, 301.1678].

(5*S*,8*R*,8a*R*)-8-Benzyloxy-5-(3′-oxopropyl)oxazolo[3,4-*a*]-pyridin-3-one 45

Ozone was bubbled through a solution of compound **43** (604 mg, 2.01 mmol) in methanol–CH_2Cl_2 (1:1, 50 cm^3) at −78 °C for 20 min after which dimethyl sulfide (250 mg) was added to the mixture at the same temperature. After the reaction mixture had been warmed to room temperature it was evaporated and the resulting residue was chromatographed on silica gel with hexane–ethyl acetate (2:1) as eluent to give compound **45** (513 mg, 84.2%) as colourless needles, mp 77–79 °C (hexane–ethyl acetate); $[\alpha]_D$ −62.7 (*c* 1.37, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 1747 (C=O); δ_H($CDCl_3$) 1.60–1.79 (4 H, m), 2.11–2.23 (2 H, m), 2.56 (2 H, t, *J* 7.0), 3.21 (1 H, dt, *J* 4.7, 8.3), 3.84–3.93 (1 H, m), 4.05 (1 H, dd, *J* 4.7, 8.9), 4.36 (1 H, dd, *J* 8.3, 8.9), 4.43 (1 H, d, *J* 11.6), 4.68 (1 H, d, *J* 11.6), 7.26–7.42 (5 H, m) and 9.80 (1 H, s); δ_C($CDCl_3$) 22.3, 24.3, 26.9, 40.8, 48.9, 54.2, 66.6, 70.5, 77.3, 127.7 (2 lines), 128.0, 128.5 (2 lines), 137.6, 157.2 and 200.9; *m/z* (EI), 304 (M^+ + 1) and 91 ($C_6H_5CH_2^+$) [Found (HRMS): M^+, 303.1468. Calc. for $C_{17}H_{21}NO_4$: *M*, 303.1471].

(5*S*,8*R*,8a*R*)-8-Benzyloxy-5-dodec-3′-enyloxazolo[3,4-*a*]-pyridin-3-one 46

A mixture of 1-bromobutane (294 mg, 1.42 mmol) and triphenylphosphine (3.7 mg, 1.42 mmol) was heated at reflux in toluene (3 cm^3) for 48 h after which it was evaporated under reduced pressure. The resulting phosphonium salt was dissolved in THF to which a solution of butyllithium (1.429 mol dm^{-3} hexane solution; 1 cm^3) was added at −78 °C. The mixture was stirred at the same temperature for 15 min and then for 1 h at room temperature. The resulting ylide solution was cooled to −78 °C and compound **43** (216 mg, 0.71 mmol) in THF (7 cm^3) added to it. After the mixture had been stirred at −78 °C for 1 h and then for 2 h with ice cooling, it was quenched with water and extracted with CH_2Cl_2. The extract was evaporated and the resulting residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (10:1) afforded compound **44** (186 mg, 63.3%) as a colourless oil; $[\alpha]_D$ −53.5 (*c* 0.89, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 1757 (C=O); δ_H($CDCl_3$) 0.88 (3 H, t, *J* 7.0), 1.26 (14 H, br s), 1.45–1.60 (2 H, m), 1.67–1.78 (2 H, m), 1.98–2.10 (4 H, m), 3.22 (1 H, dt, *J* 4.1, 9.5), 3.57 (1 H, dt, *J* 4.4, 8.2), 3.86–3.94 (1 H, m), 4.07 (1 H, dd, *J* 4.4, 8.9), 4.36 (1 H, dd, *J* 8.2, 8.9), 4.43 (1 H, d, *J* 11.6), 4.67 (1 H, d, *J* 11.6), 5.32–5.42 (2 H, m) and 7.29–7.38 (5 H, m); δ_C($CDCl_3$) 14.1, 22.6, 24.1, 24.4, 26.5, 27.2, 29.2, 29.3, 29.5, 29.7, 30.1, 31.9, 48.9, 54.6, 66.4, 70.7, 77.5, 127.8 (3 lines), 128.1, 128.6 (2 lines), 131.1, 137.6 and 157.0; *m/z* (EI), 413 (M^+), 322 (M^+ − 91), 246 [M^+ − $(CH_2)_2CH$=$CH(CH_2)_7CH_3$] [Found (HRMS): M^+, 413.2908. Calc. for $C_{26}H_{39}NO_3$: *M*, 413.2930].

(5*S*,8*R*,8a*R*)-5-Decyl-8-hydroxyoxazolo[3,4-*a*]pyridin-3-one 47

A mixture of compound **46** (121 mg, 0.29 mmol), methanol (30 cm^3), conc. hydrochloric acid (0.6 cm^3) and 10% Pd–C (80 mg) was shaken under atmosphere of H_2 until uptake of H_2 ceased. The catalyst was filtered off, the filtrate evaporated and the resulting residue was extracted with $CHCl_3$. The extract was washed with 5% aqueous $NaHCO_3$ and evaporated and the resulting residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (2:1) yielded compound **47** (93.5 mg, 98.2%) as colourless needles, mp 107–109 °C (lit.,[8b] 103–104 °C), $[\alpha]_D$ −19.39 (*c* 0.78, $CHCl_3$) {lit.,[8b] $[\alpha]_D^{24}$ −18.6 (*c* 0.44, $CHCl_3$)}; δ_H($CDCl_3$) 0.87 (3 H, t, *J* 7.0), 1.25 (20 H, br s), 1.47–1.50 (1 H, m), 1.57–1.75 (1 H, m), 1.86–1.95 (1 H, m),

3.40–3.52 (2 H, m), 3.82–3.90 (1 H, m), 4.25 (1 H, dd, *J* 4.2, 8.8) and 4.40 (1 H, dd, *J* 8.2, 8.8) [these ^{1}H NMR spectral results were identical with those kindly provided by Professor K. Tadano (Keio University)]; $\delta_C(CDCl_3)$ 14.1, 22.6, 26.3, 26.7, 28.4, 29.3, 29.5, 29.6 (5 lines), 29.9, 31.9, 48.9, 56.1, 66.5, 70.9 and 157.3 (Found: C, 69.65; H, 10.85; N, 4.3. $C_{19}H_{35}NO_3$ requires *C, 70.1; H, 10.85*; N, 4.3%).

Acknowledgements

We are indebted to Prof K. Tadano (Keio University) for providing the spectral data for compound **47**.

References

1 Y. Yuasa, J. Ando and S. Shibuya, *J. Chem. Soc., Chem. Commun.*, 1994, 455.
2 Y. Yuasa, J. Ando and S. Shibuya, *J. Chem. Soc., Perkin Trans. 1*, 1996, 465.
3 (*a*) E. J. Enholm and G. Prasad, *Tetrahedron Lett.*, 1989, **30**, 4939; (*b*) T. Sugawara, B. A. Otter and T. Ueda, *Tetrahedron Lett.*, 1988, **29**, 75 and references cited therein.
4 Y. Yuasa, J. Ando and S. Shibuya, *J. Chem. Soc., Chem. Commun.*, 1994, 1383.
5 Y. Yuasa, J. Ando and S. Shibuya, *Tetrahedron: Asymmetry*, 1995, **6**, 1525.
6 R. F. W. Jackson and A. B. Rettie, *Tetrahedron Lett.*, 1993, **34**, 2985.
7 Structure, (*a*) S. Shinagawa, F. Kasahara, Y. Wada, S. Harada and M. Asai, *Tetrahedron*, 1984, **40**, 3465; *synthesis*, (*b*) B. P. Bashyal, H.-F. Chow, L. E. Fellows and G. W. Fleet, *Tetrahedron*, 1987, **43**, 423; (*c*) T. Ohta, A. Hosi and S. Nozoe, *Tetrahedron Lett.*, 1988, **29**, 329; (*d*) T. Wakamiya, K. Yamanori, N. Nishikawa and T. Shiba, *Tetrahedron Lett.*, 1985, **26**, 4759; (*e*) Y. Hirai, T. Terada, Y. Amemiya and T. Momose, *Tetrahedron Lett.*, 1992, **33**, 7893; (*f*) A. G. M. Barrett and D. Pilipauskas, *J. Org. Chem.*, 1991, **56**, 2787.
8 Synthesis of prosopinine and related compounds; (*a*) K. Tadano, K. Takao, Y. Nigawara, E. Nishino, I. Tagkagi, K. Maeda and S. Ogawa, *Synlett*, 1993, 565; (*b*) K. Takao, N. Nigawara, E. Nishino, I. Takagi, K. Maeda, K. Tadano and S. Ogawa, *Tetrahedron*, 1994, **50**, 5681; (*c*) G. R. Cook, L. G. Beholtz and J. R. Stille, *Tetrahedron Lett.*, 1994, **35**, 1669; (*d*) G. R. Cook, L. G. Beholtz and J. R. Stille, *J. Org. Chem.*, 1994, **59**, 3575 and references cited therein.
9 (*a*) A. R. Pinder, *Nat. Prod. Rep.*, 1992, **9**, 491; (*b*) A. Numata and T. Ibuka, in *The Alkaloids*, ed. A. Brossi, Academic Press, New York, 1987, vol. 31, ch. 6; (*c*) G. B. Foder and B. Colasanti, *Alkaloids: Chemical and Biological Perspectives*, ed. S. W. Peppetier, Wiley, New York, 1985, vol. 3, pp. 1–90 and references cited therein.
10 K. Mori, T. Takigawa and T. Matsuo, *Tetrahedron*, 1979, **35**, 933.
11 A. Veyrieres, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1626.
12 O. Mitsunobu, M. Wada and T. Sano, *J. Am. Chem. Soc.*, 1972, **94**, 679.
13 S. Kano, Y. Yuasa, N. Mochizuki and S. Shibuya, *Heterocycles*, 1990, **30**, 263.
14 M. Larcheveque and J. Lalende, *Tetrahedron*, 1984, **40**, 1061.
15 (*a*) S. D. Rychnovsky, G. Griesgraber, S. Zeller and D. J. Skalitzky, *J. Org. Chem.*, 1991, **56**, 5161; (*b*) B. S. Wakefield, *Organolithium Methods*, Academic Press, New York, 1988, p. 46.

Paper 5/06188A
Received 19*th September* 1995
Accepted 20*th October* 1995