Tetrahedron Vol 47, No 10/11, pp 2005-2026, 1991
Printed in Great Britain

0040-4020/91 $3 00+ 00
Pergamon Press plc

SYNTHESIS OF THE HOMOCHIRAL "TRICYCLIC HEART" OF MANZAMINE A [1]

Karel M.J. Brands, Arthur A.P. Meekel and Upendra K. Pandit *

Laboratory for Organic Chemistry, University of Amsterdam

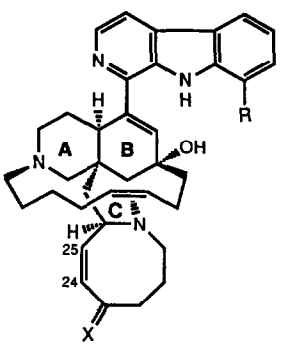
Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

(*Received in UK* 19 *November* 1990)

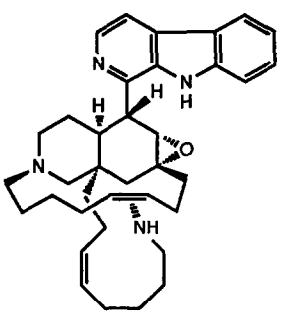
Abstract: An expedient and enantiospecific synthesis of a strategically functionalized tricyclic intermediate for the construction of manzamine A is described

Introduction

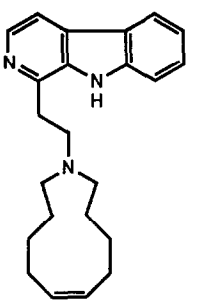
The manzamines are a new family of marine alkaloids isolated recently from three different genera of marine sponges by two independent groups [2,3] Their biological activity and novel molecular architecture has made them targets of recent synthetic efforts [4-7] We set out to develop a concise synthetic strategy, which should give access to the structurally related manzamines A (**1**), B (**2**), E (**3**) and F (**4**) as well as to their derivatives, for structure activity studies A synthesis of the structurally simplest congener, manzamine C (**5**), has recently been reported by the group of Hino [8]



1 X=H_2, R=H
3 X=O , R=H , 24,25 dihydro
4 X=O , R=OH , 24,25 dihydro



2



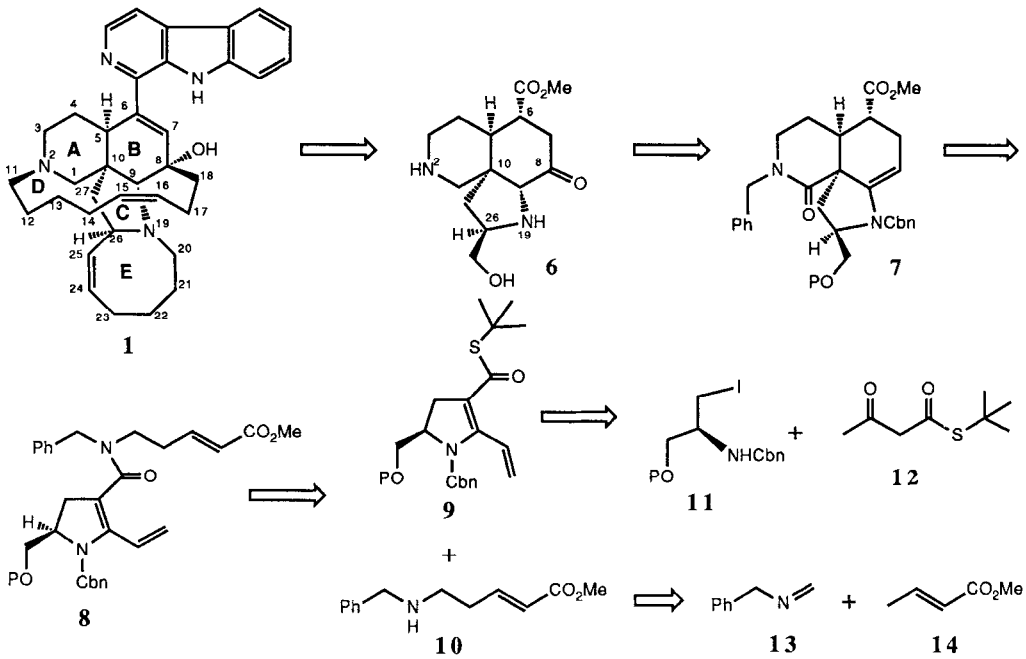
5

This report will present a detailed account of the stereoselective synthesis of an enantiomerically pure tricyclic compound, which represents the **ABC** substructure of the manzamine alkaloids and, in addition, carries adequate functional groups at stategic positions for the elaboration of (+)-manzamine A in particular [9]

Strategy

Analysis of the structure of (+)-manzamine A (**1**) shows that the **ABC** substructure contains all of the five stereogenic carbons and most of the stereochemical information of the molecule (Scheme 1) The tricyclic com-

pound **6** was regarded as an attractive subtarget, because it already contains four of the five final chiral carbons, including the crucial quaternary C-10 [10], in their required absolute configurations. Furthermore, **6** possesses adequate functionality at strategic positions for the final stages of the synthesis. The C-6 ester group forms a handle for the introduction of the β-carboline moiety. The hydroxymethyl group attached at C-26 together with N-19, and the C-8 keto group together with N-2 allow flexible access to the eight-membered **E** ring and the thirteen-membered **D** ring, respectively. The density of both the stereogenic centers and the functionalities of ring **B** evoked the application of an intramolecular Diels-Alder reaction [11] in the synthetic approach to **6**.



Scheme 1

Detailed analysis of all feasible carbocyclic intramolecular Diels-Alder reactions for the construction of the pyrrolo[2,3-*i*]isoquinoline framework of **6**, suggested the use of a *Z*-diene [12] as a stereocontrol element [13] to implement the *cis* fusion between the **A** and **B** rings. This led to the retrosynthetic transformation of **6**, *via* **7**, to triene **8**. At the outset, it was anticipated that the protected hydroxymethyl substituent at C-26 of enantiomerically pure intermediate **8** would direct the diastereoselective formation of **7** in the intramolecular cycloaddition reaction. Carbamate protection of N-19 would minimize the expected propensity towards aromatization of the 2-pyrroline part of **8**. The functional group addition at C-1 in going from **6** to **7** (replacement of methylene for carbonyl group), served two important objectives. Thermally allowed [1,5]-sigmatropic hydrogen shifts in the pentadienylic part of triene **8**, which often plague intramolecular Diels-Alder reactions of trienes incorporating *Z*-dienes [14], are not feasible. In addition, the amide functionality in **8** makes further disconnection, in a convergent manner, to the *tert*-butyl thiol ester **9** and amino ester **10** obvious. The use of thiol esters as latent reactive acyla-

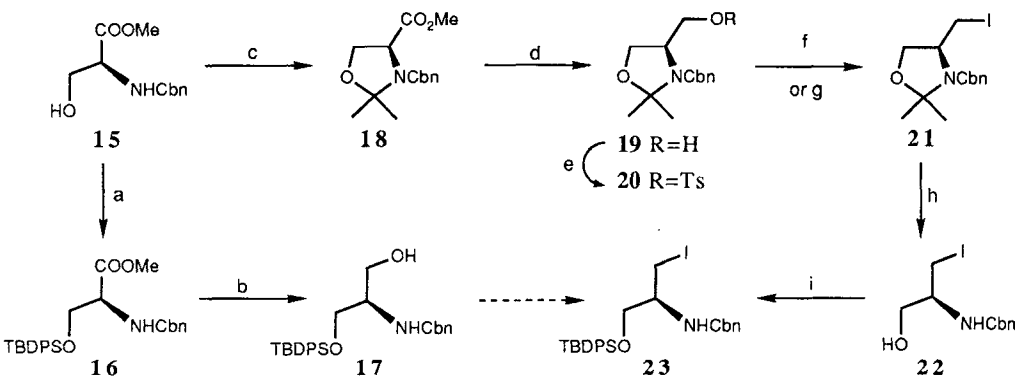
tion agents, triggered by the presence of thiophilic salts, has been pioneered by Masamune [15] and has recently also been demonstrated by Ley [16] and others [17]. Further analysis of compound **9** led to enantiomerically pure iodide **11** and *S-tert*-butyl acetothioacetate (**12**). The chirality of **11** can be mapped with both antipodes of the amino acid serine, which are cheap and readily available members of the chiral pool [18].

At the outset, the synthesis of amino ester **10** was envisaged to be the result of some kind of vinylogous Mannich-type reaction between synthetic equivalents of imine **13** and methyl crotonate (**14**).

Results and discussion

Synthesis of the enantiomerically pure iodide **23**

A straightforward route from the known *L*-serine derivative **15** [19] to iodide **23** is given in Scheme 2. Direct reduction of the reported ester **16** [20] to alcohol **17** proved, surprisingly, difficult. Reduction with excess DIBAL (in THF at room temperature) or lithium borohydride (in refluxing THF) stopped at the aldehyde oxidation level. This may be explained by invoking the formation of a stable chelate after delivery of one hydride equivalent. The problem was circumvented when ester **15** was first reduced to the corresponding aldehyde by one equivalent of DIBAL at low temperature, followed by a second reduction with excess sodium borohydride in ethanol at room temperature. As the yield of this procedure was only modest (46 %), as has been reported for a similar sequence [21], the direct approach was abandoned.



(a) TBDPSCl, imidazole, DMF; quant. (b) i DIBAL, THF; ii $NaBH_4$, EtOH; 46 % (c) dimethoxypropane, PhH, PTSA; quant. (d) $Ca(BH_4)_2$, THF/EtOH; quant. (e) TsCl, DMAP, py.; 91 % (f) NaI, acetone; 66 % (g) I_2, Ph_3P, imidazole, $PhCH_3$/MeCN; 79 % (h) conc. HCl, acetone; quant. (i) TBDPSCl, imidazole; DMF; 90 %

Scheme 2

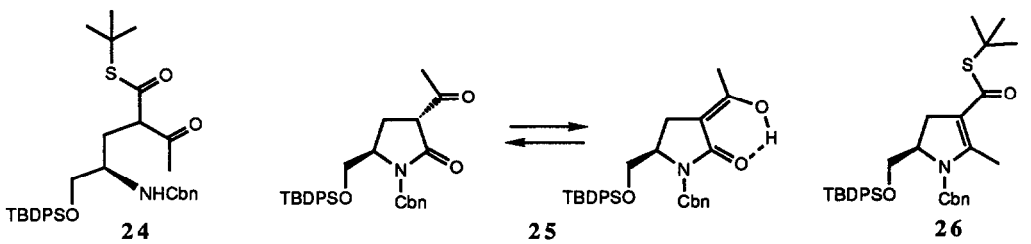
It was anticipated that the crucial reduction step would become a high yielding process if the formation of a stable chelate was prevented. Therefore an additional, temporary protection of the carbamate nitrogen atom was used. Subjection of **15** to the ketalization conditions described by Garner [22] furnished **18** quantitatively. Gratifyingly, reduction of this compound with calcium borohydride [23] provided alcohol **19** in quantitative yield. Conventional transformation of **19** into **21** *via* tosylate **20** was accomplished in only 55 % overall yield. Particularly the displacement with iodide proceeded in a modest yield. Fortunately, direct transformation of **19**

into **21**, following Garegg's procedure [24], was more rewarding (79 % yield). The conversion of **21** into the highly crystalline **23** proceeded uneventfully, in 90 % overall yield. A good indication for the optical purity of **23**, obtained *via* this sequence, was obtained by ^{1}H-NMR analysis of **22** in the presence of (+)-Eu(hfc)$_3$ [25], as only one enantiomer could be detected.

In summary, enantiomerically pure **23** was obtained from methyl (-)-*N*-(benzyloxycarbonyl)-L-serinate (**15**) in 71 % overall yield Only once in the five-step sequence chromatographic purification of an intermediate was required In addition, the approach was amenable to large scale processing of the materials (starting with 50 g of **15**), without any loss in yields

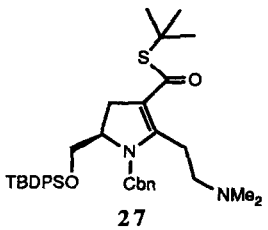
Synthesis of the 2-vinyl-2-pyrroline-3-thiol ester **30**

Stirring of **23** with 1 1 equivalents of the sodium enolate of **12** in DME at room temperature for one week (optimized conditions) led to incomplete conversion of the starting iodide Apart from residual iodide, the anticipated alkylation product **24** and lactam **25** were present in the crude reaction mixture Upon subjection of this mixture to the dehydrative conditions described by Fukuyama[26], **24** was transformed into **26**. Complete separation of the requisite **26** from unconverted **23** by flash chromatography [27] proved difficult. Fortunately, it was possible to crystallize iodide **23** selectively. The corrected yields of **26** and **25** (keto/enol 7/3) over the two steps were 49 and 17 %, respectively The acetyl appendage at 3-C of the keto tautomer of **25** was tentatively assigned to possess the thermodynamically more stable α orientation, *trans* to the silyloxymethylene group

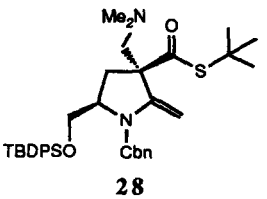


Although the yield for the synthesis of **26** was rather low, the above process was rendered synthetically efficient by recycling the recovered iodide Generally, it was preferred to subject crude **26**, contaminated with iodide **23**, to the aminomethylation reaction (*vide infra*), prior to executing a facile separation of the resulting product **27** from residual **23**

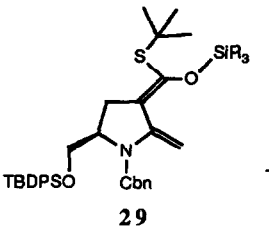
Initially, the introduction of the vinyl group was achieved *via* Danishefsky's [28] protocol Extensive experimentation showed it to be essential to generate the lithium dienolate of **26** with lithium hexamethyldisilazide in THF, in order to obtain good yields in its reaction with Eschenmoser's salt [29] Under optimized conditions, a mixture of the γ-addtion product **27** and the α-addtion product **28** was obtained in 43 and 28 % yield, respectively As only one diastereomer of **28** was formed according to its spectral data, the stereochemistry of this product was tentatively assigned as indicated above, assuming an attack of Eschenmoser's salt on the sterically less hindered α-face of the intermediate lithium dienolate of **26**



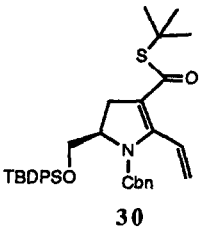
27



28

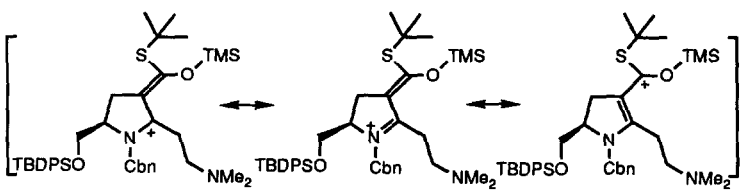


29

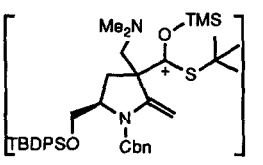


30

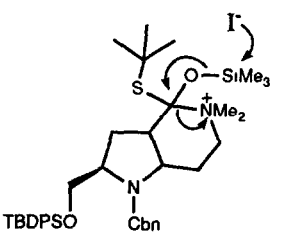
Because of the poor regioselectivity and the fact that the above reaction was not amenable to large scale processing, new Mannich-type reaction conditions for the dimethylaminomethylation of **26** were developed It was contemplated that better results might be obtained in the desired transformation, by allowing a reaction of the electrophilic Eschenmoser's salt with *O*-silylketene acetal derivative **29** Unfortunately, it was not possible to prepare the latter compound by quenching lithium dienolates of **26**, generated with LDA or LHMDS in THF, with trimethylsilyl- or *tert*-butyldimethylsilyl chloride A felicitous discovery was made, when a reaction was carried out between "*in situ* generated" **29** and the iminium salt Upon adding triethylamine, trimethylsilyl triflate and Eschenmoser's salt consecutively to a solution of **26** in dichloromethane at 0°C, a rapid and regioselective formation of **27** was observed The pivotal product could be isolated in 85 % yield. We believe that this procedure might be of general value for accomplishing the dimethylaminomethylation of weakly acidic compounds The complete regioselectivity of the above procedure is ascribed to a combination of steric and electronic factors Sterically, γ-attack of Eschenmoser's salt to intermediate **29** is the favoured process Furthermore, the intermediate arising from γ-attack (**31a**) is better stabilized than its counterpart arising form α-attack (**31b**) An alternate mechanism, which can account for the observed regioselectivity of the process, would involve a hetero Diels-Alder reaction between **29** and Eschenmoser's salt, followed by a desilylative breakdown of the resulting intermediate **32** [30]



31a



31b

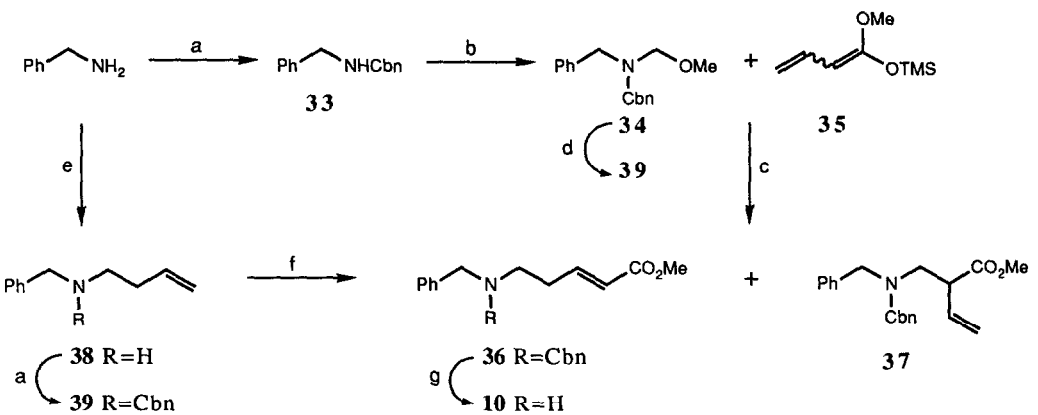


32

As the chromatographic mobilities of iodide **23** and amine **27** differed widely, as opposed to those of **23** and **26** (*vide supra*), chromatographic separation of residual **23** was preferably carried out at this stage A mixture of **26** and unconverted **23** was subjected to the new Mannich-type protocol, whereupon pure **27** was obtained together with pure **23**, which was reused for the synthesis of **26** The corrected overall yield for the three-step transformation of **23** into **27** was 57 % Quaternization of **27**, followed by DBU treatment, provided the rather unstable diene **30** in 89 % yield, setting the stage for the crucial aminolysis reaction with amino ester **10**

Synthesis of the amino ester **10**

In the last decade *N*-acyliminium ions have been used as synthetic equivalents of imines in Mannich-type reactions with silyl enol ethers [31] The *N*-acyliminium precursor **34** was readily available from **33** [32], by alkylation with methoxymethyl chloride (Scheme 3) Treatment of **34** with **35** [33] in dichloromethane in the presence of two equivalents of BF_3 Et_2O provided a 1 1 mixture of the regioisomeric amino esters **36** and **37**, in 77 % combined yield The poor regioselectivity under optimized conditions prompted the investigation of a different approach, which was inherently regioselective Reaction of **34** with allyltrimethylsilane provided the homoallylic amine **39** quantitatively The same compound was obtained in a more straightforward manner by alkylation of benzylamine with 4-bromo-1-butene, followed by acylation of **38** with benzyl chloroformate (88 % overall yield) Ozonolysis and Wittig chemistry furnished **36** (*E*/*Z* 15/1) in 76 % overall yield Deprotection with hydrogen bromide in glacial acetic acid, under carefully controlled conditions, provided the requisite **10** (92 % yield) During the deprotection procedure the *Z* isomer of **10** spontaneously lactamized to *N*-benzyl-5,6-dihydro-1*H*-pyridone As this compound does not interfere in the aminolysis reaction, which is described in the sequel, an excess of **10**, contaminated with the afore mentioned pyridone (approximately 5 mol%), was generally used in these reactions

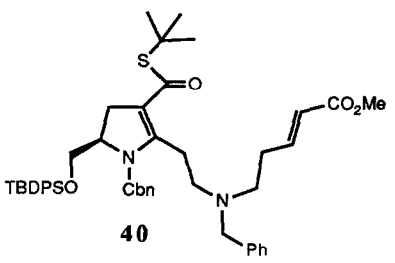


(a) CbnCl, $NaHCO_3$ (b) NaH, MOMCl, DMF, 74 % (c) 2eq BF_3 Et_2O, CH_2Cl_2, 77 % (d) allylTMS, BF_3 Et_2O, CH_2Cl_2, quant (e) 4-butenylbromide, 88 % (f) i O_3, ii Zn, AcOH, iii Ph_3PCHCO_2Me, 76 % (g) HBr, HOAc , 92 %

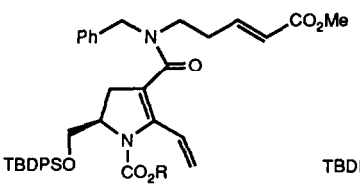
Scheme 3

Synthesis of the tricyclic "heart" of manzamine A

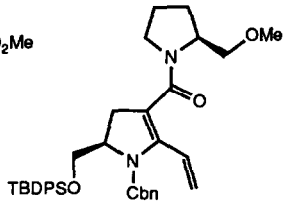
Reaction of thiol ester **30** with amino ester **10** in the presence of silver triflate as an activator and diisopropylethylamine as an acid scavenger, furnished **41** in 65-70 % yield It was shown that the aminolysis reaction occurs *via* a Michael-type adduct Compound **40** is produced in a fast primary step In a relatively slow second step, the tertiary amine of **40** intramolecularly attacks the thiolester carbon, which is activated by silver triflate This mechanism is supported by the following observations In an analogous reaction the Michael type intermediate could be isolated in high yield when the thiol ester activator was omitted, and addition of silver triflate to this intermediate yielded the anticipated triene [34] In addition, 2-pyrroline-3-thiol esters lacking an electrophilic 2-vinyl group (e g **26**), failed to react with secondary amines under the above conditions



40



41

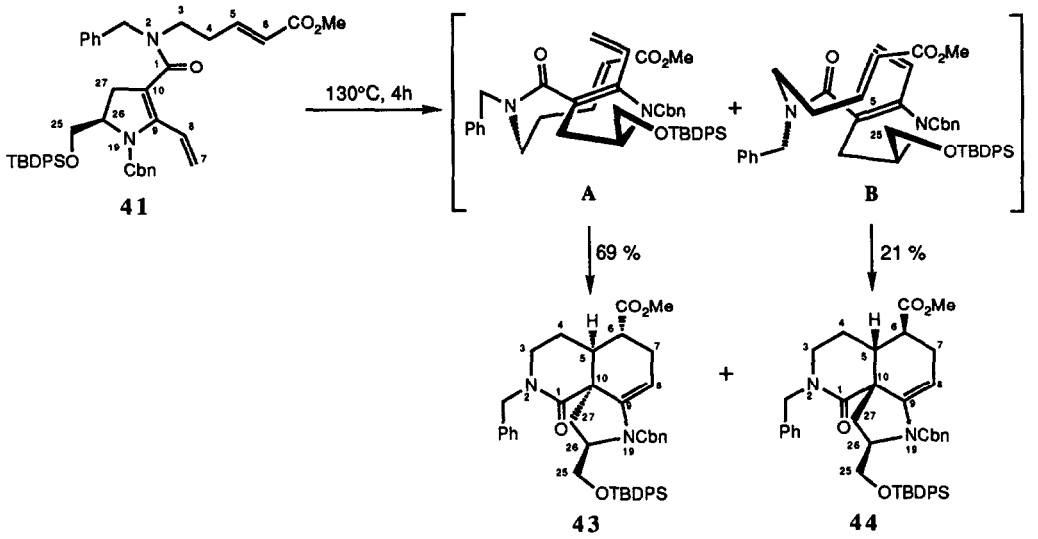


42

Up to this stage the optical purity of all new compounds could be related to the demonstrated optical purity of (-)-**15** (by optical means) and (+)-**22** (by spectroscopic means) As no synthetic manipulations near the sole chiral carbon had been conducted, it was confidently assumed that triene **41** was optically pure However, to obtain independent proof for this surmise, thiol ester **30** was aminolysed with commercially-obtained (*S*)-(+)-2-(methoxymethyl)pyrrolidine under the standard conditions Both ^{1}H- and ^{13}C-NMR spectra (recorded in toluene-d_8 at 90°C to offset the appearance of rotamers due to restricted rotation around the amide bond) of the resulting **42** (obtained in 86 % yield) showed only a single set of absorptions, thus confirming the optical purity of **41** [25]

The intramolecular Diels-Alder reaction of **41** yielded two diastereomeric products (3 5 1), to which structures **43** and **44** have been assigned, in 90 % combined yield (Scheme 4) The diastereomeric transition states **A** and **B** can be envisaged for this reaction As anticipated, the main product **43** is formed via transition state **A** Transition state **B** is disfavoured as a result of strong non-bonded interactions between the vinylic H-5 and C-25 methylene hydrogen atoms The assigned structures of **43** and **44** rested mainly upon NMR spectra, which were recorded in benzene-d_6 at 65°C to offset the appearance of rotamers due to the restricted rotation around the carbamate bond Their interpretation was facilitated by the corresponding data for a model tricyclic compound [4] and COSY experiments Characteristic differences in the spectra of **43** and **44** were found for the protons attached to C-27 and the vinylic H-8 In compound **43** H-27$_{exo}$, H-27$_{endo}$ and H-8 were found at 1 61, 2 65 and 6 42 ppm, respectively, whereas in compound **44** these protons resonated at 1 97, 2 22 and 5 97 ppm Dreiding models offer an explanation for this As a result of steric repulsion between the silyloxymethylene group and and the lactam carbonyl group in compound **43**, π-orbital overlap between the carbamate chromofore and the double bond is somewhat decreased, in comparison to compound **44** Consequently, H-8 in **44**, which

is attached to a carbon with higher electron density than in **43**, is found 0 45 ppm more upfield than in **43** The above mentioned steric repulsion also causes H-27$_{endo}$ in **43** to move into the deshielding cone of the lactam carbonyl group, and H-27$_{exo}$ to move out of the shielding cone of the enecarbamate double bond, as opposed to the corresponding protons in **44** In addition, the dihedral angle between H-27$_{endo}$ and H-26 in **43** becomes approximately 90°, which causes the former to resonate as a doublet (^2J 13 2 Hz) In compound **44**, H-27$_{endo}$ is found as a double doublet (^2J 12 4 and ^3J 7 2 Hz)



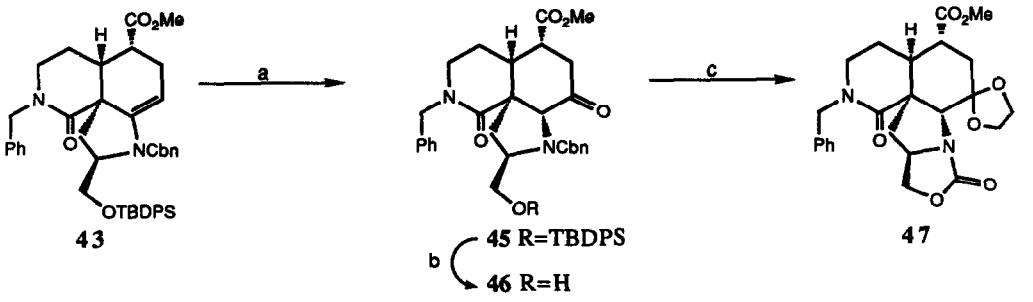
Scheme 4

The stereochemistry of the diastereomers was further substantiated by NOE experiments Irradiation in **43** of H-5 at 1 92 ppm gave an enhancement for H-7$_{ax}$ at 2 34 ppm, and for H-27$_{exo}$ at 1 61 ppm Irradiation of H-27$_{endo}$ at 2 65 ppm gave an enhancement for one of the silyloxymethylene protons at 4 40 ppm Conversely, irradiation of of both silyloxymethylene protons at 4 40 and 4 47 ppm gave only an enhancement for H-27$_{endo}$ As expected, irradiation in **44** of H-27$_{endo}$ at 2 22 ppm did not result in NOE effects Irradiation of H-27$_{exo}$ at 1 97 ppm gave an enhancement for H-5 at 2 09 ppm However, irradiation of H-5 or one of the silyloxymethylene protons at 3 91 ppm did not result in any enhancements Eventually, these structure assignments were corroborated by the X-ray data of a derivative of **43** (*vide infra*)

The major diastereomer **43** was converted into the tricyclic ketone **45** in 78 % yield, by stoichiometric dioxyosmylation [35] and, after reductive workup, acid catalyzed dehydration Conventional desilylation of **45** provided alcohol **46** in high yield Irradiation of one the hydroxymethylene protons (multiplet at 4 06 ppm) in **46** resulted only in an enhancement of H-9 (singlet at 5 23 ppm), thus establishing the thermodynamically favoured, equatorial orientation of H-9 in these compounds

In preliminary studies directed towards the elaboration of **46** towards manzamine A, protection of its keto group was required Subjection of **46** to forcing ketalization conditions, provided the unexpected oxazolidone **47** in low yield This highly crystalline compound allowed corroboration of all structure assignments, which

were hitherto solely made on the basis of spectral data, by X-ray analysis Figure 1 shows the result of this analysis [38]



Scheme 5

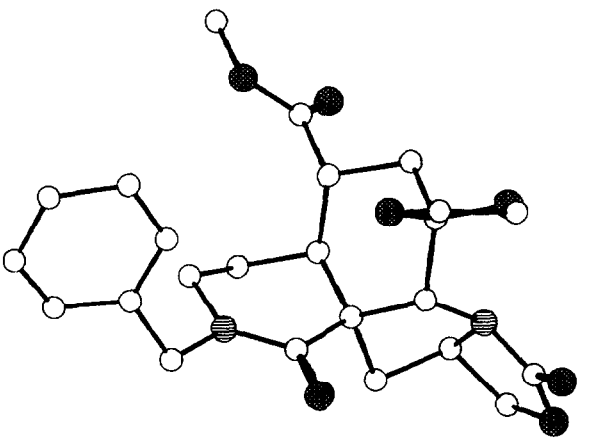


Figure 1 PLUTO drawing of **47**

The enantiomerically pure tricyclic compound **45**, which represents the ABC substructure of the manzamine alkaloids and, in addition carries adequate functional groups at strategic positions for the elaboration of manzamine A in particular, was stereoselectively synthesized from L-(+)-serine in 13 steps, and 11 8 % overall yield Elaboration of this compound into (+)-manzamine A is actively being pursued in our laboratory and will be reported in due course.

Experimental

General information IUPAC nomenclature is followed in naming the compounds[39] Infrared (IR) spectra were recorded on a Perkin Elmer 298 spectrophotometer and are reported in cm^{-1} Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on Bruker AC-200 or Bruker WM-250 instruments The Bruker instruments were also used for recording carbon nuclear magnetic resonance (^{13}C-NMR) spectra (50 and 62 9 MHz, respectively) Chemical shifts are given in ppm downfield of tetramethylsilane (TMS) Coupling constants (*J*) are given in Hertz (Hz) As is indicated ^{1}H-NMR shift correlation spectroscopy (COSY), attached proton test (APT), double resonance and ^{1}H-^{13}C correlation experiments were occasionally used for signal assignments Mass spectra were obtained on a Varian MAT 711 instrument. Ionization techniques are given as EI (electron impact, 70 eV ionization energy used, intensity of most important and/or abundant peaks are given between brackets as percentage of the base peak), FD (field desorption) or FI (field ionization, temperature used indicated between brackets) Mass peaks are given in m/z Accurate mass measurements were performed on a Varian MAT 711 instrument Thin layer chromatography (TLC) was performed using silicagel coated plastic sheets (Merck silicagel 60 F_{254}) and UV and/or iodine for detection Chromatographic purification refers to flash chromatography using Merck silica gel 60 (230-400 mesh) [27] Silica Woelm (70-150 mesh) was used for silica gel plug filtration Commonly, mixtures of ethyl acetate (EA) and hexanes (Hex) were used as eluents Melting points (m p) were determined on a Leitz melting point microscope and are uncorrected Boiling points (b p) are also uncorrected When necessary, reactions were performed in oven dried (overnight at 140°C) glassware under a nitrogen atmosphere in absolute solvents Reagents were purified before use when appropriate Commercially obtained Eschenmoser's salt was purified immediately before use, by washing it repeatedly with THF until white, and drying *in vacuo* Commercially obtained solutions of *n*-butyllithium in hexanes were titrated before use according to a literature procedure[40]

For the description of the NMR spectra of compounds **41** and **43-47** manzamine A numbering[3] is used

Methyl (+)-*N*-(benzyloxycarbonyl)-*O*-(*tert*-butyldiphenylsilyl)-L-serinate (16) [20] To a solution of 2 53 g of **15** (10 0 mmol) in 5 ml of DMF were added 2 80 g of *tert*-butyldiphenylsilyl chloride (98 %, 10 0 mmol) and 750 mg of imidazole (11 0 mmol) After stirring at ambient temperature for 45 minutes the suspension was poured into 75 ml of ether/hexanes 2/1 and washed with 1M hydrochloric acid (10 ml), saturated $NaHCO_3$ solution (10 ml), water (10 ml) and brine (10 ml) The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*, yielding 5 03 g of **16** (10 2 mmol, quant., pure according to NMR) as a colourless oil, $[\alpha]_D$ +8 2° (c 1 2, CH_2Cl_2), **IR** ($CHCl_3$) 3435 (m), 1740 (sh), 1718 (s), 1500 (s), 1339 (s), 1108 (s), 1100 (sh), 815 (m), 692 (s), **^{1}H-NMR** ($CDCl_3$, 250 MHz) 1 02 (s, 9H, Si^{t}Bu), 3 73 (s, 3H, OCH_3), 3 90 (dd, *J* 10 2, *J* 3 0, 1H, CHH'OSi), 4 09 (dd, *J* 10 2, *J* 2 8, 1H, CHH'OSi), 4 44 (ddd, *J* 8 4, *J* 3 0, *J* 2 8, 1H, CHN), 5 11 (s, 2H, OCH_2Ph), 5 65 (d, *J* 8 3, 1H, $NHCO_2$), 7 37 (m, 11H, Ar), 7 58 (m, 4H, ortho SiArH), **MS** (EI) 448 (4 %), 434 (29 %), 390 (5 %), 356 (6 %), 326 (6 %), 284 (7 %), 240 (7 %), 213 (13 %), 194 (25 %), 183 (8 %), 162 (10 %), 135 (12 %), 91 (100 %)

(+)-*N*-(Benzyloxycarbonyl)-*O*-(*tert*-butyldiphenylsilyl)-L-serinol (17) To a solution of 5 93 g of **16** (11 3 mmol) in 50 ml of THF at -78°C was added 14 0 ml of a 1 0 M DIBAL/THF solution (14 0 mmol) in 5 minutes After stirring at -75°C for 16 hours, 5 0 ml of ethanol was added and the temperature allowed to rise to room temperature before the reaction mixture was concentrated *in vacuo* The residue was dissolved in 75 ml of ethanol and 2 60 g of sodium borohydride (69 mmol) was added After stirring for 6 hours at ambient temperature 100 ml of water were added. The mixture was acidified to pH 2 with 3M hydrochloric acid. The water layer was extracted with ethyl acetate (4x25 ml) The combined organic layers were washed with saturated $NaHCO_3$ solution (2x20 ml), water (15 ml) and brine (15 ml), dried ($MgSO_4$) and concentrated *in vacuo* Chromatography (Hex/EA 6/1, Hex/EA 1/1) of the residue yielded (in order of elution) 0 73 g of recovered **16** (1 5 mmol) and 2 10 g of **17** (4 5 mmol, 40 %) Corrected yield 46 %, $[\alpha]_D$ +1 8° (c 1 5, CH_2Cl_2), **IR** ($CHCl_3$) 3440 (m), 1710 (s), 1500 (s), 1420 (m), 1110 (s), 1100 (m), 818 (m), 695 (s), **^{1}H-NMR** ($CDCl_3$, 250 MHz) 1 05 (s, 9H, Si^{t}Bu), 2 29 (br, 1H, OH), 3 66-3 80 (m, 5H, CH_2OH, CH_2OSi and CHN), 5 08 (s, 2H, OCH_2Ph), 5 31 (br, 1H, $NHCO_2$), 7 37 (m, 11H, Ar), 7 62 (m, 4H, ortho SiArH), **MS** (EI) 406 (3 %), 298 (6 %), 220

(14 %), 199 (17 %), 183 (8 %), 177 (8 %), 108 (84 %), 107 (64 %), 91 (45 %), 79 (100 %)

3-Benzyl-4-methyl (-)-(*S*)-2,2-dimethyloxazolidine-*N*,4-dicarboxylate (18) A solution of 36 3 g of **15** (143 3 mmol), 50 ml of 2,2-dimethoxypropane (400 mmol) and 625 mg of *p*-toluenesulfonic acid monohydrate (3 3 mmol) in 600 ml of benzene was refluxed for one hour via a Dean-Stark trap and then concentrated to a volume of 200 ml After 200 ml of ether had been added to the cooled solution, the organic layer was washed with saturated $NaHCO_3$-solution (2x50 ml), water (50 ml) and brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo* Silica gel plug filtration (Hex/EA 6/1) of the dark oil yielded 42 11 g of **18** (144 mmol, quantitative) as a yellow oil, which was as such used for the next step A small sample of this product was purified by chromatography (Hex/EA 5/1), $[\alpha]_D$ -49 5° (c 2 0, CH_2Cl_2), **IR** ($CHCl_3$) 2990 (m), 2940 (m), 2880 (m), 1750 (s), 1705 (s), 1405 (s), 1350 (s), 1220 (br), 1090 (s), 1068 (s), 1050 (s), 833 (m), 690 (m), **^{1}H-NMR** ($CDCl_3$, 250 MHz, mixture of rotamers 2/1) 1 48 and 1 55 (s, 3H, CMeMe'), 1 63 and 1 69 (s, 3H, CMeMe'), 3 62 and 3 76 (s, 3H, OCH_3), 4 07 (dt, *J* 9 2, *J* 2 8, 1H, OCHH'CHN), 4 15 (dd, *J* 9 2, *J* 6 7, 1H, OCHH'CHN), 4 46 and 4 54 (dd, *J* 6 7, *J* 2 8, 1H, OCHH'CHN), 5 09 and 5 18 (AB, 2H, OCH_2Ph), 7 30 (m, 5H, Ar), **MS** (EI) 293 (M^+, 1 %), 278 (11 %), 234 (12 %), 190 (1 %), 91 (100 %)

Benzyl (-)-(*R*)-2,2-dimethyl-4-(hydroxymethyl)oxazolidine-*N*-carboxylate (19) To an ice-cold suspension of 12 0 g of powdered calcium chloride (108 mmol) and 8 2 g of sodium borohydride (217 mmol) in 80 ml of THF was added a solution of 21 50 g of **18** (73 3 mmol) in 80 ml of ethanol After stirring for three hours at 5 °C, the suspension was poured onto 100 g of crushed ice and 100 ml of saturated ammonium chloride solution and 200 ml of ethyl acetate were added (vigorous carbon dioxide evolution !) The slurry was stirred for 30 minutes before 50 ml of concentrated hydrochloric acid was added slowly The water layer was extracted with 100 ml of ethyl acetate The combined organic layers were washed with saturated $NaHCO_3$ solution (100 ml), water (100 ml) and brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo*, yielding 19 40 g of **19** (73 1 mmol, quant) This product was pure according to NMR and used as such for the next step A small sample was purified by chromatography (Hex/EA 2/1), $[\alpha]_D$ -19 5° (c 1 0, CH_2Cl_2), **IR** ($CHCl_3$) 3440 (br), 1690 (s), 1410(s), 1350 (s), 1070 (s), 690 (m), **^{1}H-NMR** ($CDCl_3$, 250 MHz, mixture of rotamers, broadened signals) 1 46 and 1 52 (s, 3H, CMeMe'), 1 52 and 1 60 (s, 3H, CMeMe'), 2 45 (br, 1H, OH), 3 59-3 83 (m, 3H, CH_2OH and OCH_2CHN), 3 99-4 12 (m, 2H, OCH_2CHN), 5 11 (m, 2H, OCH_2Ph), 7 34 (m, 5H, Ar), **MS** (EI) 265 (M^+, 0 5 %), 250 (40 %), 234 (17 %), 206 (10 %), 190 (11 %), 91 (100 %)

Benzyl (-)-(*S*)-2,2-dimethyl-4-[(*p*-toluenesulfonyl)oxymethyl)]oxazolidine-*N*-carboxylate (20) To an ice-cold solution of 19 3 g of **19** (72 7 mmol) and 700 mg of dimethylaminopyridine (5 7 mmol) in 100 ml of dichloromethane and 15 ml of pyridine was added 14 1 g of *p*-toluenesulfonyl chloride (74 0 mmol) portionwise, over a period of two hours After stirring for 24 hours at 0 °C and two hours at ambient temperature, the reaction mixture was diluted with 300 ml of ether The organic layer was washed with 1M hydrochloric acid (1x100 ml, 2x50 ml), saturated $NaHCO_3$ solution (50 ml), water (50 ml) and brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo* Chromatography (Hex/EA 10/1, Hex/EA 5/1, Hex/EA 2/1) of the residue yielded 25 17 g of **20** (60 0 mmol, 83 %) as a white solid, m p 82-86 °C and 1 89 g of recovered **19** (7 1 mmol) Corrected yield 91 %, $[\alpha]_D$ -39 0° (c 1 0, CH_2Cl_2), **IR** ($CHCl_3$) 1700 (s), 1403(s), 1362 (s), 1350 (s), 1170 (s), 1090 (s), 981 (s), 821 (m), 809 (m), 690 (m), 650 (m), **^{1}H-NMR** ($CDCl_3$, 200 MHz, mixture of rotamers) 1 42 and 1 49 (s, 3H, CMeMe'), 1 49 and 1 53 (s, 3H, CMeMe'), 2 43 (s, 3H, $ArCH_3$), 3 78-4 00 (m, 3H, CH_2OSO_2 and OCH_2CHN), 4 11 (m, 2H, OCH_2CHN), 5 08 (m, 2H, OCH_2Ph), 7 33 (m, 7H, Ar), 7 68 and 7 79 (d, *J* 8 1, 2H, ortho ArH)

Benzyl (+)-(*S*)-2,2-dimethyl-4-(iodomethyl)oxazolidine-*N*-carboxylate (21)

from **20** A suspension of 38 0 g of **20** (90 6 mmol) and 38 0 g of sodium iodide (254 mmol) in 100 ml of acetone was refluxed for 20 hours The cooled reaction mixture was poured into 400 ml of ether and washed with water (100 ml), 10 % sodium thiosulfate

solution (2x75 ml) and brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo* Silica gel plug filtration (Hex/EA 10/1, Hex/EA 2/1) of the residue yielded 22 51 g of **21** (60 0 mmol, 66 %) as a yellow oil and 3 93 g of recovered crystalline **20** (9 4 mmol) Corrected yield. 74 %

from **19** A solution of 9 50 g of **19** (35 8 mmol), 22 50 g of triphenylphosphine (85.8 mmol, 2 4 eq), 6 60 g of imidazole (96 9 mmol, 2 7 eq) and 17.30 g of iodine (68 2 mmol, 1.9 eq) in 100 ml of benzene and 50 ml of acetonitrile was refluxed for 90 minutes To the ice-cold reaction mixture were added 100 ml of toluene, 100 ml of saturated $NaHCO_3$ and 5.0 ml of 35 % hydrogen peroxide solution The organic layer was washed with 10 % sodium thiosulfate solution (3x75 ml) The combined aqueous layers were extracted with 50 ml of toluene. The combined organic layers were washed with 10 % sodium thiosulfate solution (50 ml), saturated $NaHCO_3$ solution (50 ml) and brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo* Silica gel plug filtration (Hex/EA 10/1) of the residue yielded 10 60 g of **21** (28 3 mmol, 79 %) as a colourless oil; $[\alpha]_D$ +10 6° (c 1 1, CH_2Cl_2), **IR** ($CHCl_3$) 1704 (s), 1408(s), 1380 (m), 1369 (m), 1355 (sh), 1349 (s), 1095 (s), 1030 (m), 830 (m), 696 (m), **^{1}H-NMR** ($CDCl_3$, 250 MHz, mixture of rotamers) 1 42 and 1 48 (s, 3H, C<u>Me</u>Me'), 1 57 and 1 63 (s, 3H, CMe<u>Me'</u>), 3 09-3 57 (m, 2H, CH_2I), 4 03 (m, 2H, OCH_2CHN), 4 22 (m, 1H, OCH_2C<u>H</u>N), 5 14 (m, 2H, OCH_2Ph), 7 35 (m, 5H, Ar), **MS** (EI) 375 (M^+, 0 5 %), 360 (16 %), 315 (4 %), 91 (100 %)

(+)-(*S*)-2-(Benzyloxycarbonyl)amino-3-iodopropan-1-ol (22) A solution of 9 70 g of **21** (25 9 mmol) in 25 ml of acetone and 15 ml of concentrated hydrochloric acid was stirred for 16 hours at room temperature The reaction mixture was diluted with 100 ml of ether and washed with water (10 ml), saturated $NaHCO_3$ solution (2x20 ml) and brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*, yielding 8.62 g of **22** (25 7 mmol, 99 %, pure according to NMR) as a yellow oil A small sample of this product was crystallised from ether/hexanes, yielding white crystals, m p 54-57 °C, $[\alpha]_D$ +15 5° (c 1 0; CH_2Cl_2), **IR** ($CHCl_3$) 3430 (m), 1710 (s), 1500 (s), 1220 (br), 1100 (m), 1050 (m), 690 (m), **^{1}H-NMR** ($CDCl_3$, 250 MHz) 2 22 (br, 1H, OH), 3 35 (m, 2H, CH_2I), 3 68 (m, 2H, CH_2OH), 3 82 (m, 1H, CHN), 5 10 (s, 2H, OCH_2Ph), 5 2 (br, 1H, $NHCO_2$), 7 34 (m, 5H, Ar), **MS** (EI) 335 (M^+, 2 %), 304 (5 %), 260 (3 %), 218 (4 %), 178 (4 %), 127 (8 %), 108 (12 %), 91 (100 %)

(+)-(*S*)-*O*-(*tert*-Butyldiphenylsilyl)-3-iodo-2-(benzyloxycarbonyl)aminopropan-1-ol (23) To an ice-cold solution of 6 42 g of **22** (19 2 mmol) and 1 63 g of imidazole (23 9 mmol) in 20 ml of DMF was added, in one portion, 5 90 g of *tert*-butyldiphenylsilyl chloride (98 %, 21 0 mmol) After stirring for one hour at room temperature, 20 ml of water and 200 ml of ether/hexanes 2/1 were added. The organic layer was washed with 0 5M hydrochloric acid (20 ml), saturated $NaHCO_3$ solution (20 ml), water (20 ml) and brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*, yielding 11 5 g of white crystals Recrystallisation from ether yielded 9 88 g of **23** (17 2 mmol, 90 %) as white crystals, m p 98-99 °C, $[\alpha]_D$ +17 3° (c 1 0, MeOH), $[\alpha]_D$ +12 8° (c 1 0, CH_2Cl_2), **IR** ($CHCl_3$) 3438 (m), 3061 (m), 3000 (m), 2950 (m), 2930 (m), 2855 (m), 1717 (s), 1498 (s), 1421 (m), 1110 (s), 1100 (sh), 818 (m), 693 (s), **^{1}H-NMR** ($CDCl_3$, 250 MHz) 1 05 (s, 9H, Si^{t}Bu), 3 42 (m, 2H, CH_2I), 3 61 (dd, *J* 9 8, *J* 5 3, 1H, C<u>H</u>H'OSi), 3 73 (m, 1H, CHN), 3 84 (dd, *J* 9 8, *J* 3 8, 1H, CH<u>H</u>'OSi), 5 03 (d, *J* 8 8, 1H, N<u>H</u>CO_2), 5 08 (s, 2H, OCH_2Ph), 7 35 (m, 11H, Ar), 7 63 (m, 4H, ortho SiAr<u>H</u>), **MS** (EI) 516 (14 %), 472 (4 %), 304 (11 %), 298 (10 %), 220 (30 %), 199 (11 %), 183 (18 %), 181 (16 %), 177 (16 %), 117 (15 %), 91 (100 %)

Benzyl (*R*)-5-[(*tert*-butyldiphenylsilyl)oxymethyl]-3-[(*tert*-butylthio)carbonyl]-4,5-dihydro-2-methyl-1*H*-pyrrole-1-carboxylate (26) and (+)-(3*R*, 5*R*)-3-Acetyl-*N*-(benzyloxycarbonyl)-5-[(*tert*-butyldiphenylsilyl)-oxymethyl]-2-pyrrolidone (25) To an ice-cold suspension of 400 mg of sodium hydride (57 %, 9 60 mmol) in 4 ml of DME was added slowly a solution of 1 75 g of **12** (10 0 mmol) in 2 ml of DME The resulting solution was stirred at ambient temperature for 15 minutes before a solution of 5 80 g of **23** (10 1 mmol) in 8 ml of DME was added After stirring for 7 days at room temperature, 50 ml of ether was added The organic layer was washed with water (3x15 ml) and brine (15 ml), dried ($MgSO_4$) and concentrated *in vacuo* The crude product was dissolved in 60 ml of toluene and 390 mg of quinoline (3 0 mmol) and 380 mg of *p*-

toluenesulfonic acid monohydrate (2 0 mmol) were added. The reaction mixture was refluxed for 30 minutes via a Dean-Stark trap, and then concentrated *in vacuo* Chromatography with gradient elution (Hex/EA 20/1, Hex/EA 10/1, Hex/EA 4/1) of the residue yielded (in order of elution) 1 77 g of pure **26** (2.9 mmol) as a colourless oil, 1 62 g of a mixture of **26** and **23** and 0 80 g of pure **25** (1 5 mmol) as a colourless oil The second fraction yielded, after crystallisation from ether/pentane, 0 80 g of **23** (1 4 mmol) as white crystals, and 0 80 g of pure **26** (1 3 mmol) as a colourless oil In total 2 57 g of **26** (4.3 mmol) were obtained. Corrected yields for **26** and **25** were 49 and 17 % respectively, R_f values (Hex/EA 4/1) for **26**, **23** and **25** are, respectively 0 46, 0 41 and 0 16, **25**. $[\alpha]_D$ +28 5° (c 1 3, CH_2Cl_2), **IR** ($CHCl_3$) 2955 (m), 2930 (m), 2860 (m), 1784 (s), 1745 (sh), 1720 (s), 1680 (sh), 1635 (w), 1584 (w), 1290 (s), 1110 (s), 1022 (m), 818 (m), 695 (s), **^{1}H-NMR** ($CDCl_3$, 250 MHz, keto/enol tautomers 7/3) 0 99 (s, 2 7H, Si^{t}Bu enol), 1 03 (s, 6 3H, Si^{t}Bu keto), 1 92 (s, 0 9H, C=CCH_3 enol), 2 02 (m, 0 7H, 4-H keto), 2 17 (m, 0 3H, 4-H enol), 2 44 (s, 2 1H, COCH_3), 2 70 (m, 1H, 4-H' keto/enol), 3 70 (m, 1H, CHH'OSi keto/enol), 3 85 (dd, *J* 10 5, *J* 4 2, 0 3H, CHH'OSi enol), 3 94 (dd, *J* 10 9, *J* 3 1, 0 7H, CHH'OSi keto), 4 02 (dd, *J* 10 5, *J* 9 1, 0 7H, 3-H keto), 4 22 (m, 1H, 5-H keto/enol), 5 14 (m, 2H, OCH_2Ph keto/enol), 7 37 (m, 11H, Ar), 7 58 (m, 4H, ortho SiArH), 10 14 (s, 0 3 H, OH enol), **^{13}C-NMR** ($CDCl_3$, 62 9 MHz, keto/enol tautomers, assignment with ATP) 19 1 (s, SiCMe_3 keto), 21 0 (s, SiCMe_3 enol), 22 9 (t, 4-C keto), 24 1 (t, 4-C enol), 26 6 (q, SiCMe_3 enol), 26 8 (q, SiCMe_3 keto), 29 2 (q, C=CCH_3 enol), 30 3 (q, COCH_3 keto), 56 3 (d, 5-C keto), 56 7 (d, 3-C keto), 57 0 (d, 5-C enol), 64 6 (t, CH_2OSi enol), 65 0 (t, CH_2OSi keto), 67 8 (t, OCH_2Ph enol), 68 2 (t, OCH_2Ph keto), 100 0 (s, 3-C enol), 127 7-130 0 (d, 10x CH aromatic keto/enol), 132 4-134 9 (s, 4x C aromatic keto/enol), 135 4 and 135 5 (d, 2x CH aromatic keto/enol), 150 8 (s, C=O carbamate keto), 151 4 (s, C=O carbamate keto), 167 5, 169 4 and 172 2 (s, C=COH enol and C=O lactam keto/enol), 201 9 (s, C=O keto), **MS** (FI, 130°C) 530 (M^++H), **26** **IR** ($CHCl_3$) 2955 (m), 2930 (m), 2860 (m), 1715 (s), 1630 (m), 1590 (s), 1396 (s), 1380 (s), 1360 (s), 1190 (s), 1178 (s), 1160 (s), 1110 (s), 693 (s), **^{1}H-NMR** ($CDCl_3$, 250 MHz) 1 02 (s, 9H, Si^{t}Bu), 1 52 (s, 9H, S^{t}Bu), 2 58 (s, 3H, 2-CH_3), 2 92 (m, 2H, 4-H_2), 3 64 (dd, *J* 10 2, *J* 2 8, 1H, CHH'OSi), 3 78 (dd, *J* 10 2, *J* 4 9, 1H, CHH'OSi), 4 32 (m, 1H, 5-H), 5 00 (AB, *J* 12 3, OCH_2Ph), 7 30 (m, 11H, Ar), 7 61 (m, 4H, ortho SiArH), **^{13}C-NMR** ($CDCl_3$, 62 9 MHz, assignment with ATP) 15 2 (q, 2-CH_3), 19 2 (s, SiCMe_3), 26 7 (q, SiCMe_3), 30 1 (q, SCMe_3), 30 8 (s, SCMe_3), 47 6 (t, 4-C), 60 1 (d, 5-C), 64 8 (t, CH_2OSi), 67 5 (t, OCH_2Ph), 117 3 (s, 3-C), 127 7-129 9 (d, 5x CH aromatic), 133 3 (s, C aromatic), 135 5 (d, CH aromatic), 135 6 (s, C aromatic), 150 4 (s, 2-C), 152 7 (s, C=O carbamate), 189 1 (s, C=O thiol ester) , **MS** (FI, 110°C) 601 (M^+)

Benzyl (+)-(*R*)-5-[(*tert*-butyldiphenylsilyl)oxymethyl]-3-[(*tert*-butylthio)carbonyl]-4,5-dihydro-2-[2-(dimethylamino)ethyl]-1*H*-pyrrole-1-carboxylate (27) and (3*S*, 5*R*)-*N*-(Benzyloxycarbonyl)-5-[(*tert*-butyldiphenylsilyl)oxy-methyl]-3-[(*tert*-butylthio)carbonyl]-3-[(dimethylamino)methyl]-2-methylidene-pyrrolidine (28)

27 and **28** *via* lithium dienolate procedure To a solution of 565 µl of HMDS (2 68 mmol) in 5 ml of THF was added at -78°C 1 70 ml of a 1 55 M *n*-BuLi/hexane solution (2 64 mmol) After stirring for 15 minutes at -78°C a solution of 1 340 g of **26** (2 23 mmol) in 2 5 ml of THF was added over a period of 6 minutes The resulting yellow solution was stirred for 30 minutes at -78°C, before 653 mg of Eschenmoser's salt (3 53 mmol) was added in one portion The resulting solution was stirred at -78°C for 10 minutes and at -30°C for 30 minutes After adding 35 ml of ether and 15 ml of saturated $NaHCO_3$ solution, the organic layer was washed with water (10 ml) and brine (10 ml), dried ($MgSO_4$) and concentrated *in vacuo* Chromatography (Hex/EA 4/1, Hex/EA 1/1, EA) of the residue yielded (in order of elution) 419 mg of **28** (0 64 mmol, 29 %) and 623 mg of **27** (0 95 mmol, 43 %), both as colourless oils

27 from **23** *via* **26**, *via* trimethylsilyl triflate procedure **(A)** Iodide **23** was converted into crude **26**, in two identical batches, as follows To an ice-cold suspension of 1 35 g of sodium hydride (57 %, 32 0 mmol) in 15 ml of DME was slowly added a solution of 6 0 g of **12** (34 mmol) in 10 ml of DME The resulting solution was stirred at ambient temperature for 15 minutes, before a solution of 15 45 g of **23** (26 9 mmol) in 45 ml of DME was added After stirring for 10 days at room temperature, the two identical batches were poured in 400 ml of ether The organic layer was washed with water (75 ml), brine (75 ml), dried ($MgSO_4$) and concen-

trated *in vacuo* The crude product was dissolved in 300 ml of toluene and 2 0 g of quinoline (15 5 mmol) and 2 0 g of *p*-toluenesulfonic acid monohydrate (10.5 mmol) were added. The reaction mixture was refluxed for 45 minutes *via* a Dean-Stark trap, and then concentrated *in vacuo* Chromatography with gradient elution (Hex/EA 20/1, Hex/EA 10/1, Hex/EA 3/1) of the residue yielded (in order of elution) 24 11 g of impure **26** (contaminated with starting **23**, according to NMR), 3 04 g of recovered **23** (5 3 mmol) and 2 00 g of pure **25** (3 8 mmol, 7 %), (B) The above obtained crude **26** was converted into **27**, in two identical batches, as follows. To an ice-cold solution of 12 05 g of crude **26** in 50 ml of dichloromethane were added successively, 3 5 ml of triethylamine (25 0 mmol), 4 2 ml of trimethylsilyl triflate (21 8 mmol) and 7.0 g of Eschenmoser's salt (37 8 mmol) After stirring for one hour at room temperature, the two batches were poured in 250 ml of ether The organic layer was washed with saturated $NaHCO_3$-solution (30 ml), water (30 ml) and brine (30 ml), dried ($MgSO_4$) and concentrated *in vacuo* Chromatographic purification of the residue yielded, in order of elution, 4 55 g of recovered **23** (7 9 mmol) and 15 15 g of pure **27** (23 0 mmol, 43 % from **23**) as a yellowish oil Total recovered **23** 7 59 g (13 2 mmol) Corrected overall yield for synthesis of **27** from **23**· 57 %, **27** $[\alpha]_D$ +50 3° (c 1 1, CH_2Cl_2), **IR** ($CHCl_3$)· 2955 (s), 2930 (sh), 2855 (m), 1710 (s), 1630 (m), 1586 (s), 1400 (s), 1180 (s), 1160 (s), 1110 (s), 830 (m), 692 (s), **^{1}H-NMR** ($CDCl_3$, 250 MHz) 1 01 (s, 9H, Si^{t}Bu), 1 51 (s, 9H, S^{t}Bu), 2 22 (s, 6H, NMe_2), 2 49 (m, 2H, $CH_2CH_2NMe_2$), 2 88 (m, 2H, 4-H_2), 3.31 (m, 2H, $CH_2CH_2NMe_2$), 3 61 (dd, *J* 10 2, *J* 3 4, 1H, CHH'OSi), 3 71 (dd, *J* 10 2, *J* 5 5, 1H, CHH'OSi), 4 32 (m, 1H, 5-H), 5 03 (AB, *J* 12 2, OCH_2Ph), 7 30 (m, 11H, Ar), 7 60 (m, 4H, ortho SiArH), **28** $[\alpha]_D$ -0 4° (c 1 8, CH_2Cl_2), **IR** ($CHCl_3$) 2955 (s), 2925 (sh), 2855 (m), 1705 (s), 1680 (sh), 1660 (s), 1630 (sh), 1450 (m), 1394 (s), 1358 (s), 1110 (s), 692 (s), **^{1}H-NMR** ($CDCl_3$, 250 MHz) 1 03 (s, 9H, Si^{t}Bu), 1 41 (s, 9H, S^{t}Bu), 2 24 (s, 6H, NMe_2), 2 35 (dd, *J* 13 3, *J* 8 3, 1H, 4-H), 2 50 (d, *J* 13 4, 1H, CHH'NMe_2), 2 88 (d, *J* 13 4, 1H, CHH'NMe_2), 2 94 (dd, *J* 13 3, *J* 4 3, 1H, 4-H'), 3 67 (dd, *J* 9 8, *J* 8 1, 1H, CHH'OSi), 3 82 (dd, *J* 9 8, *J* 3 6, 1H, CHH'OSi), 4 17 (m, 1H, 5-H), 4 75 (s, 1H, C=CHH'), 4 97 (AB, *J* 12 3, OCH_2Ph), 5 61 (br, 1H, C=CHH'), 7 33 (m, 11H, Ar), 7 60 (m, 4H, ortho SiArH)

Benzyl (+)-(*R*)-5-[(*tert*-butyldiphenylsilyl)oxymethyl]-3-[(*tert*-butylthio)carbonyl]-4,5-dihydro-2-vinyl-1*H*-pyrrole-1-carboxylate (30) To a solution of 1 94 g of **27** (2 94 mmol) in 10 ml of acetonitrile at -20°C was added 510 mg of methyl iodide (3 59 mmol) The cooling bath was removed and the mixture was stirred at ambient temperature for one hour, before it was concentrated *in vacuo* The residue was dissolved in 13 ml of dichloromethane and 475 mg of DBU (96 %, 3 00 mmol) was added at 0°C After stirring for 90 minutes at room temperature, the reaction mixture was concentrated *in vacuo* Silica gel plug filtration (Hex/EA 6/1) yielded 1 614 g of **30** (2 63 mmol, 89 %) as a colourless oil, $[\alpha]_D$ +86 0° (c 0 9, CH_2Cl_2), **IR** ($CHCl_3$) 3000 (m), 2955 (s), 2925 (m), 2855 (m), 1715 (s), 1635 (m), 1615 (m), 1582 (m), 1555 (s), 1395 (s), 1359 (s), 1280 (s), 1239 (s), 1175 (s), 1160 (s), 1110 (s), 833 (m), 692 (s), **^{1}H-NMR** ($CDCl_3$, 250 MHz) 1 00 (s, 9H, Si^{t}Bu), 1 49 (s, 9H, S^{t}Bu), 2 99 (m, 2H, 4-H_2), 3 65 (dd, *J* 10 2, *J* 3 7, 1H, CHH'OSi), 3 75 (dd, *J* 10 2, *J* 5 5, 1H, CHH'OSi), 4 40 (m, 1H, 5-H), 5 04 (AB, *J* 12 2, 2H, OCH_2Ph), 5 52 (m, *J* 11 5, 1H, CH=CH_{cis}), 5 53 (m, *J* 17 3, 1H, CH=CH_{trans}), 6 90 (m, *J* 17 3, *J* 11 5, 1H, CH=$CH_{cis}H_{trans}$), 7 30 (m, 11H, Ar), 7 60 (m, 4H, ortho SiArH)

Benzyl *N*-benzyl-*N*-(methoxymethyl)carbamate (34) To a suspension of 19 00 g of sodium hydride (57 %, washed with pentane 3x50 ml, 455 mmol) in 200 ml of DMF at room temperature was added slowly over 45 minutes, a solution of 95 7 g of benzyl *N*-(benzyl)carbamate [32] (397 mmol) in 100 ml of THF The temperature rose to 50°C After stirring for another 30 minutes, the solution was cooled with an ice bath and 80 0 ml of methoxymethyl chloride (1075 mmol) was added at such a rate that the temperature did not rise above 30°C After stirring the resulting solution overnight at ambient temprature, 600 ml of water were added The aqueous layer was extracted with ether (3x200 ml) The combined organic layers were washed with water (100 ml) and brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo* Silica gel plug filtration (Hex/EA 10/1) of the residue, yielded 84 05 g of **34** (295 mmol, 74 %) as a colourless oil, **IR** ($CHCl_3$) 2990 (m), 2935 (m), 1690 (s), 1444 (m), 1415 (s), 1280 (s), 1220 (s), 1126 (s), 1082 (s), 1068 (m), 688 (s), **^{1}H-NMR** ($CDCl_3$, 200 MHz, broad signals, 5/4 mixture of rotamers) 3 25 and 3 33 (s, 3H, OCH_3), 4 57 (s, 2H, NCH_2Ph), 4 72 and 4 78 (s, 2H, NCH_2O), 5 21 (s, 2H, OCH_2Ph), 7 31 (m, 10H, Ar)

Methyl (*E*)-[*N*-benzyl-*N*-(benzyloxycarbonyl)amino]-2-pentenoate (36) and Methyl (±)-2-{[*N*-benzyl-*N*-(benzyloxycarbonyl)amino]methyl}-3-butenoate (37)

36 and **37** from **34**. To an ice-cold solution of 2 55 g of **34** (8 94 mmol) in 15 ml of dichloromethane was added 2.2 ml of freshly distilled boron trifluoride etherate (17 9 mmol) After 10 minutes 2.50 ml of **35** (13 0 mmol) was added. The yellow solution was stirred at room temperature for 3 hours, before 20 ml of saturated $NaHCO_3$-solution and 50 ml of dichloromethane were added. The organic layer was washed with saturated $NaHCO_3$-solution (20 ml), water (20 ml) and brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo* Chromatography (Hex/EA 5/1) of the residue yielded (in order of elution) 1 18 g of **37** (3.34 mmol, 37 %) and 1.26 g of **36** (3 57 mmol, 40 %)

36 from **39** Ozone was passed through a solution of 8 30 g of **39** (28 1 mmol) in 75 ml of dichloromethane and 5 ml of methanol at -78°C, until the colour changed from colourless to light blue (approximately 2.5 hours) For 5 minutes nitrogen was bubbled through the solution, followed by the addition of 10 0 g of zinc powder and 6 ml of acetic acid. The grey suspension was slowly warmed to room temperature over 2 hours, filtered over celite and concentrated *in vacuo* The residue was dissolved in 100 ml of ether and washed with saturated $NaHCO_3$-solution (2x20 ml), water (20 ml) and brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*, yielding 8 34 g of a colouress liquid A solution of 11 6 g of methyl (triphenylphosphoranylidene)acetate (35.0 mmol) in 50 ml of dichloromethane was added to a solution of this product in 100 ml of dichloromethane. After stirring at room temperature overnight, the reaction mixture was concentrated *in vacuo* The residue was taken up in 100 ml of ether. The crystals were filtered and the filtrate was concentrated *in vacuo* Chromatography (Hex/EA 6/1) of the residue yielded 7.55 g of **36** (21 4 mmol; 76 %) as a colourless oil, **36**. **IR** ($CHCl_3$) 3000 (m), 2950 (m), 1718 (sh), 1690 (s), 1655 (sh), 1282 (m), 1120 (m), **^{1}H-NMR** ($CDCl_3$, 250 MHz, broad signals) 2 38 (m, 2H, NCH_2CH_2CH=C), 3 35 (m, 2H, NCH_2CH_2CH=C), 3 70 (s, 3H, OCH_3), 4.49 (s, 2H, NCH_2Ph), 5 17 (s, 2H, OCH_2Ph), 5 77 (t, *J* 16 8, 1H, CH=CHCO_2), 6 83 (m, 1H, CH=$CHCO_2$), 7.28 (m, 10H, Ar); **37**: **IR** ($CHCl_3$) 3000 (m), 2950 (m), 1728 (s), 1690 (s), 1640 (w), **^{1}H-NMR** ($CDCl_3$, 250 MHz, broad signals): 3.52 (m, 2H, NCH_2CHCO_2), 3 64 (m, 3H, OCH_3), 3 71 (m, 1H, NCH_2CHCO_2), 4 52 (m, 2H, NCH_2Ph), 5 10 (m, 2H, CH=CH_2), 5 19 (s, 2H, OCH_2Ph), 5 78 (m, 1H, CH=CH_2), 7 29 (m, 10H, Ar)

***N*-benzyl-*N*-(3-butenyl)amine (38)** A mixture of 50 0 ml of benzylamine (460 mmol), 15 3 g of potassium carbonate (110 mmol) and 13 0 g of 4-butenyl bromide (97 %, 93 mmol) was heated at 70°C overnight. Filtration of the reaction mixture and fractionation yielded 13 2 g of **38** (82 mmol, 88 %, pure according to NMR) as a colourless liquid, and recovered benzylamine, b p 100-120°C at 13 mmHg. **IR** ($CHCl_3$) 3075 (m), 1630 (m), 1450 (s), 915 (s), **^{1}H-NMR** ($CDCl_3$, 200 MHz) 1 62 (s, 1H, NH), 2 29 (dt, J 13 6, J 6 8, 2H, NCH_2CH_2), 2 72 (t, J 6 8, 2H, NCH_2CH_2), 3 81 (s, 2H, NCH_2Ph), 5 07 (m, 2H, CH=CH_2), 5 80 (ddt, J 17 1, J 10 2, J 6 8, 1H, CH=CH_2), 7 35 (m, 5H, Ar)

Benzyl *N*-benzyl-*N*-(3-butenyl)carbamate (39)

from **34** To an ice cold solution of 45.0 g of **34** (158 mmol) and 37 0 ml of allyltrimethylsilane (233 mmol) in 200 ml of dichloromethane was added in 15 minutes 23 0 ml of freshly distilled boron trifluoride etherate (187 mmol) After stirring at 0°C for 150 minutes, the solution was poured into 400 ml of ether The organic layer was washed with saturated $NaHCO_3$-solution (3x100 ml), water (100 ml) and brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo*, yielding 46 0 g of **39** (155 mmol, 98 %, pure according to NMR) as a yellow liquid

from **37** To an ice cold solution of 9 70 g of **38** (60 mmol) in 70 ml of 1,4-dioxane and 6 ml of saturated $NaHCO_3$ solution was added slowly over one hour 11 0 g of benzyl chloroformate (96 %, 61 9 mmol) After stirring the resulting solution for one hour at room temperature, it was poured into 300 ml of ether and 75 ml of water The organic layer was washed with 1M hydrochloric acid (75 ml), saturated $NaHCO_3$-solution and brine (75 ml), dried ($MgSO_4$) and concentrated *in vacuo*, yielding 17 7 g of **39** (60 0 mmol, quant), **IR** ($CHCl_3$) 3050 (w), 1675 (s), 1630 (w), 1410 (s), 1355 (m), 907 (m), **^{1}H-NMR** ($CDCl_3$, 250 MHz, signals broadened) 2 27 (m, 2H, NCH_2CH_2CH=CH_2), 3 31 (m, 2H, NCH_2CH_2CH=CH_2), 4 51 (s, 2H, NCH_2Ph), 5 01 (m, 2H,

CH=CH_2), 5 19 (s, 2H, OCH_2Ph), 5 70 (m, 1H, CH=CH$_2$), 7 30 (m, 10H, Ar)

Methyl (*E*)-5-(benzylamino)-2-pentenoate (10) A solution of 1 02 g of **36** (2 89 mmol) in 5 ml of 30 % hydrogen bromide in acetic acid was stirred for 50 minutes at room temperature and then poured onto 35 g of crushed ice. The aqeous phase was extracted with ethyl acetate (3x10 ml), basified to pH 11 and extracted with ethyl acetate (3x15 ml) The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*, yielding 581 mg of **10** (2 65 mmol, 92 %) According to NMR, crude **10** contained up to 5 % of *N*-Benzyl-5,6-dihydro-1*H*-2-pyridone, **11**. **IR** ($CHCl_3$) 1715 (s), 1650 (m), 1433 (m), 1281 (m), 1165 (m), 980 (m), **^{1}H-NMR** ($CDCl_3$, 200 MHz) 1 65 (s, 1H, NH), 2 43 (dtd, *J* 6 9, *J* 1 1, 2H, NCH$_2$CH_2CH=C), 2 78 (t, *J* 6 9, 2H, NCH_2CH$_2$CH=C), 3 73 (s, 3H, OCH_3), 3 80 (s, 2H, NCH_2Ph), 5 89 (dt, *J* 15 7, *J* 1 4, 1H, CH=CHCO$_2$), 6 96 (dt, *J* 15 7, *J* 7 1, 1H, CH=CHCO$_2$), 7 31 (m, 10H, Ar), ***N*-Benzyl-5,6-dihydro-1*H*-2-pyridone IR** ($CHCl_3$). 2995 (m), 1658 (s), 1601 (m), 1480 (s), 1448 (m), 1245 (m), 1140 (m), 815 (s), 690 (m), **^{1}H-NMR** ($CDCl_3$, 200 MHz) 2 33 (tdd, *J* 7 1, *J* 4 2, *J* 1 9, 2H, 5-H_2), 3 32 (t, *J* 7 1, 2H, 6-H_2), 4 63 (s, 2H, NCH_2Ph), 6 00 (dt, *J* 9 8, *J* 1 8, 1H, 3-H), 6 55 (dt, *J* 9 8, *J* 4 2, 1H, 4-H), 7 29 (m, 5H, Ar)

Benzyl (+)-(*R*)-3-{[*N*-benzyl-*N*-((*E*)-4-carbomethoxy-3-butenyl)]carbamyl}-5-[(*tert*-butyl-diphenylsilyl)oxymethyl]-4,5-dihydro-2-vinyl-1*H*-pyrrole-1-carboxylate (41) A solution of 1 53 g of **30** (2 49 mmol), 680 mg of **10** (3 10 mmol), 770 mg of diisopropylethylamine (6 0 mmol) and 710 mg of silver trifluoromethanesulfonate (2 76 mmol) in 14 ml of acetonitrile was stirred for 18 hours at room temperature The resulting dark suspension was filtered over a short three layer column, consisting (from bottom to top) of Celite, silica Woelm and Florisil The column was eluted with ethyl acetate The filtrates were concentrated *in vacuo*, and the residue chromatographed (Hex/EA 3/1), yielding 1 24 g of **41** (1 67 mmol, 67 %) as a yellowish oil, **IR** ($CHCl_3$) 2950 (m), 2930 (sh), 2855 (m), 1705 (s), 1650 (sh), 1640 (sh), 1605 (s), 1398 (s), 1110 (s), 691 (s), **^{1}H-NMR** (C_6D_6, 65°C, 250 MHz) 1 10 (s, 9H, Si^{t}Bu), 2 08 (m, 2H, 4-H_2), 2 86 (m, 2H, 27-H_2), 3 21 (m, 2H, 3-H_2), 3 42 (s, 3H, OCH_3), 3 72 (m, 2H, 25-H_2), 4 32 (m, 3H, NCH_2Ph and 26-H), 4 95 (AB, *J* 12 3, 2H, OCH_2Ph), 5 18 (d, *J* 11 9, 1H, 7-H_{cis}), 5 66 (d, *J* 17 3, 1H, 7-H_{trans}), 5 72 (d, *J* 15 6, 1H, 6-H), 6 78 (m, 2H, 5-H and 8-H), 7 15 (m, 16H, Ar), 7 65 (m, 4H, ortho SiArH)

Benzyl (+)-(2'*S*, 5*R*)-[(*tert*-butyldiphenylsilyl)oxymethyl]-4,5-dihydro-3-{[(2'-methoxymethyl)pyrrolidin-1'-yl]carbonyl}-2-vinyl-1*H*-pyrrole-1-carboxylate (42) To a solution of 535 mg of **30** (0 87 mmol) in 6 ml of acetonitrile were added 161 µl of commercially-obtained (*S*)-(+)-2-(methoxymethyl)pyrrolidine (1 30 mmol), 379 µl of diisopropylethylamine (2 17 mmol) and 246 mg of silver trifluoromethanesulfonate (0 96 mmol) After stirring at ambient temperature for 20 hours, the dark suspension was filtered over a short three layer column, consisting (from bottom to top) of Celite, silica Woelm and Florisil The column was eluted with ethyl acetate The filtrates were concentrated *in vacuo* and the residue chromatographed (Hex/EA 1/1), yielding (in order of elution) 58 mg of recovered **30** (0 09 mmol) and 429 mg of **42** (0 67 mmol, 77 %) as a colourless oil Corrected yield 86 %, $[\alpha]_D$ +31 7° (c 0 9, CH_2Cl_2), **IR** ($CHCl_3$) 2990 (m), 2955 (m), 2930 (m), 2855 (m), 1703 (s), 1635 (sh), 1590 (s), 1392 (s), 1353 (s), 1110 (s), 693 (s), **^{1}H-NMR** (C_7D_8, 90°C, 250 MHz) 1 31 (s, 9H, Si^{t}Bu), 1 58 (m, 1H, 3'-H), 1 85 (m, 3H, 3'-H, 4'-CHH'), 2 92 (ddd, *J* 16 6, *J* 3 0, *J* 1 6, 1H, 4-H), 3.27 (ddd, *J* 16 6, *J* 10 0, *J* 1 6, 1H, 4-H'), 3 32 (s, 3H, OCH_3), 3 42 (m, 2H, 5'-CHH'), 3 54 (dd, *J* 9 3, *J* 5 6, 1H, 6'-H), 3 60 (dd, *J* 9 3, *J* 3 8, 1H, 6'-H'), 3 98 (dd, *J* 9 9, *J* 7 0, 1H, 6-H), 4 06 (dd, *J* 9 9, *J* 4 3, 1H, 6-H'), 4 37 (m, 1H, 5-H), 4 58 (m, 1H, 5'-H), 5 18 (AB, *J* 12 4, 2H, OCH_2Ph), 5 30 (dd, *J* 11 3, *J* 1 7, 1H, 8-H_{cis}), 5 76 (dd, *J* 17 6, *J* 1 7, 1H, 8-H_{trans}), 6 93 (ddt, *J* 17 6, *J* 11 3, *J* 1.6, 1H, 7-H), 7 20 (m, 11H, Ar), 7 60 (m, 4H, ortho SiArH), **^{13}C-NMR** (C_6D_6, 65°C, 62 9 MHz, assignment with ATP) 20 3 (s, SiCMe$_3$), 25 0 (t, 3'-C or 4'-C), 28 0 (q, SiCMe$_3$), 28 8 (t, 3'-C or 4'-C), 34 9 (t, 4-C), 47 5 (t, 5'-C), 57 4 (d, 2'-C), 59 4 (d, 5-C), 60 5 (q, OCH_3), 65 8 (t, 6-C), 68 0 (t, OCH_2Ph), 74 0 (t, 6'-C), 118 6 (s, 2-C or 8-C), 119 8 (s, 2-C or 8-C), 128 8-130 7 (6xd, 5x CH aromatic and 7-C), 134 9 (2xs, CH aromatic and 3-C), 136 7 (d, CH aromatic), 137 7 (s, C aromatic), 154 1 (s, C=O carbamate), 166 8 (s, C=O amide)

8-Benzyl-5-methyl (-)-(4a*S*, 5*R*, 9*R*, 10a*S*)-2-benzyl-9-[(*tert*-butyldiphenylsilyl)oxymethyl]-1-oxo-2,3,4,4a,5,6,9,10-octahydro-pyrrolo[2,3-*i*]isoquinoline-5,8(1*H*)-dicarboxylate (43) and 8-Benzyl-5-methyl (+)-(4a*R*, 5*S*, 9*R*, 10a*R*)-2-benzyl-9-[(*tert*-butyldiphenylsilyl)oxy-methyl]-1-oxo-2,3,4,4a,5,6,9,10-octahydro-pyrrolo[2,3-*i*]isoquinoline-5,8(1*H*)-dicarboxylate (44) The glassware for this reaction was rinsed with HMDS and dried at 150°C overnight. A solution of 250 mg of **41** (0.34 mmol) in 10 ml of deoxygenated xylenes was refluxed for four hours and then concentrated *in vacuo* Chromatography (Hex/EA 3/1) of the residue yielded (in order of elution) 173 mg of **43** (0 23 mmol, 68 %) and 52 mg of **44** (0.07 mmol; 21 %), both as colourless oils, **43**. $[\alpha]_D$ -54 3° (c 1 0; CH_2Cl_2), **IR** ($CHCl_3$) 3000 (m), 2950 (m), 2925 (sh), 2850 (m), 1724 (s), 1708 (s), 1670 (sh), 1635 (s), 1398 (s), 1322 (s), 1110 (s), 818 (m), 693 (s), **^{1}H-NMR** (C_6D_6, 65°C, 250 MHz, assignment with COSY) 1 17 (s, 9H, Si^{t}Bu), 1 51 (m, 1H, H_{4ax}), 1 61 (dd, *J* 13 2, *J* 9 4, 1H, H_{27exo}), 1 70 (m, 1H, H_{4eq}), 1 92 (dt, *J* 11 6, *J* 3 3, 1H, H_5), 2 34 (m, 2H, H_{7eq} and H_{7ax}), 2 55 (m, 1H, H_6), 2 65 (d, *J* 13 2, 1H, H_{27endo}), 2 78 (ddd, *J* 12.0, *J* 7 1, *J* 1 3, 1H, H_{3eq}), 3 05 (ddd, *J* 12 0, *J* 6 4, 1H, H_{3ax}), 3 26 (s, 3H, OCH_3), 4 15 (d, *J* 14 4, 1H, NCHH'Ph), 4 26 (m, 1H, H_{26}), 4 40 (m, 1H, H_{25}), 4 47 (m, 1H, $H_{25'}$), 4 56 (d, *J* 14 4, 1H, NCHH'Ph), 4 98 (AB, *J* 12 4, 2H, OCH_2Ph), 6 42 (m, 1H, H_8), 7 10 (m, 16H, Ar), 7 75 (m, 4H, ortho SiArH), **^{13}C-NMR** (C_6D_6, 65°C; 62 9 MHz, assignment with ATP and C-H correlation experiments) 20 4 (s, SiCMe3), 23 0 (t, C_4), 28 1 (q, SiCMe3), 28 6 (t, C_7), 38 1 (t, C_{27}), 41 4 (d, C_6), 42 7 (d, C_5), 44 1 (t, C_3), 51 0 (s, C_{10}), 51 1 (t, NCH_2Ph), 51 8 (q, OCH_3), 61 6 (d, C_{26}), 64 9 (t, C_{25}), 67 7 (t, OCH_2Ph), 103 7 (d, C_8), 129.3-130 6 (d, 8x CH aromatic), 135 5 (s, C aromatic), 136 6 (d, CH aromatic), 137 9 (s, C_9), 138 8 and 140 8 (s, 2x C aromatic), 153 6 (s, NCO_2Bn), 172 8 (s, CO_2Me), 175 5 (s, C_1), **MS** exact mass observed: 742 3450, calc for $C_{45}H_{50}N_2O_6Si$ 742.3438, **44**. $[\alpha]_D$ +89.3° (c 0 9, CH_2Cl_2), **IR** ($CHCl_3$) 3000 (m), 2950 (m), 2925 (m), 2850 (m), 1720 (s), 1711 (s), 1685 (sh), 1629 (s), 1401 (s), 1303 (s), 1159 (s), 1110 (s), 815 (m), 692 (s), **^{1}H-NMR** (C_6D_6, 65°C, 250 MHz, assignment with COSY) 1 18 (s, 9H, Si^{t}Bu), 1 60 (m, 1H, H_{4ax}), 1 67 (m, 1H, H_{4eq}), 1 97 (dd, *J* 12 4, *J* 9 1, 1H, H_{27exo}), 2 09 (dt, *J* 11 8, *J* 3 2, 1H, H_5), 2 22 (dd, *J* 12 4, *J* 7 2, 1H, H_{27endo}), 2 37 (m, 2H, H_{7eq} and H_{7ax}), 2 64 (m, 1H, H_6), 2 75 (m, 1H, H_{3eq}), 3 17 (ddd, *J* 12 5, *J* 5 8, 1H, H_{3ax}), 3 28 (s, 3H, OCH_3), 3 91 (m, 1H, H_{25}), 4 06 (d, *J* 14 3, 1H, NCHH'Ph), 4 17 (m, 1H, $H_{25'}$), 4 50 (m, 1H, H_{26}), 4 68 (d, *J* 14 3, 1H, NCHH'Ph), 5 11 (AB, *J* 12 7, 2H, OCH_2Ph), 5 97 (m, 1H, H_8), 7 15 (m, 16H, Ar), 7 70 (m, 4H, ortho SiArH), **^{13}C-NMR** (C_6D_6, 65°C, 62 9 MHz, assignment with ATP) 20 4 (s, SiCMe3), 23 4 (t, C_4), 28 0 (q, SiCMe3), 29 1 (t, C_7), 39 8 (t, C_{27}), 41 7 (d, C_5 and C_6), 43 9 (t, C_3), 50 8 (t, NCH_2Ph), 51 1 (s, C_{10}), 51 8 (q, OCH_3), 60 6 (d, C_{26}), 65 8 (t, C_{25}), 67 9 (t, OCH_2Ph), 108 3 (d, C_8), 128 8-130 6 (d, 8x CH aromatic), 135 2 (s, C aromatic), 136 7 (d, CH aromatic), 138 3 (s, C_9), 139 0 and 140 9 (s, 2x C aromatic), 171 5 (s, CO_2Me), 175 4 (s, C_1), **MS** exact mass observed 742 3450, calc. for $C_{45}H_{50}N_2O_6Si$ 742 3438

8-Benzyl-5-methyl (+)-(4a*S*, 5*R*, 7a*R*, 9*R* 10a*S*)-2-benzyl-9-[(*tert*-butyldiphenylsilyl)oxymethyl]-1,7-dioxo-2,3,4,4a,5,6,7a,9,10-nonahydro-pyrrolo[2,3-*i*]isoquinoline-5,8(1*H*)-dicarboxylate (45) To a solution of 1 00 g of **43** (1 35 mmol) in 4 ml of pyridine was added 3 75 ml of a 0 393 M osmium tetraoxide/pyridine solution (1 47 mmol) The resulting dark solution was stirred at room temperature for 16 hours, before a solution of 1 0 g of sodium pyrosulfite in 8 ml of water was added. After stirring for 4 hours, 25 ml of 10 % hydrochloric acid were added under ice cooling and the resulting solution was extracted with chloroform (3x15 ml) The combined organic layers were washed with 1M hydrochloric acid (10 ml), water (10 ml) and brine (10 ml), and dried ($MgSO_4$) The solution was filtered over a short column of Florisil The column was eluted with ethyl acetate and the combined filtrates were concentrated *in vacuo* A solution of the resulting product and 20 mg of *p*-toluenesulfonic acid monohydrate in 30 ml of benzene was refluxed for 30 minutes, and then concentrated *in vacuo* Chromatography of the residue yielded 795 mg of **45** (1 05 mmol, 78 %) as a white foam, $[\alpha]_D$ +20 3° (c 2 7, dichloromethane), **IR** ($CHCl_3$) 1730 (s), 1698 (s), 1635 (s), 1422 (s), 1417 (s), 1357 (m), 1288 (m), 1172 (m), 1111 (s), 820 (w), 694 (s), **^{1}H-NMR** (C_7D_8, 90 °C, 250 MHz, assignment with COSY) 1 38 (s, 9H, Si^{t}Bu), 1 57 (m, 1H, H_{4eq}), 1 84 (m, 1H, H_{4ax}), 2 03 (m, 1H, H_{27}), 2 14 (m, *J* 11 1, 1H H_5), 2 45 (m, 1H, H_{7eq}), 2 83 (m, 3H, H_6, H_{7ax} and $H_{27'}$), 2 94 (ddd, *J* 12 1, *J* 5 8, *J* 3 4, 1H, H_{3eq}), 3 22 (ddd, *J* 12 1, *J* 11 1, *J* 5 2, 1H, H_{3ax}), 3 48 (s, 3H, OCH_3), 4 31 (m, 3H, H_{25}, $H_{25'}$ and H_{26}), 4 54 (AB, *J* 14 4, 2H, NCH_2Ph), 5 18 (m, 2H, OCH_2Ph), 5 33 (s,

1H, H_9), 7 30 (m, 16H, Ar), 7 95 (m, 4H, ortho SiArH); MS (FD) 758 (M^+)

8-Benzyl-5-methyl (-)-(4a*S*, 5*R*, 7a*R*, 9*R*, 10a*S*)-2-benzyl-2,3,4,4a,5,6,7,7a,9,10-decahydro-1,7-dioxo-9-(hydroxymethyl)-pyrrolo[2,3-*i*]isoquinoline-5,8(1*H*)-dicarboxylate (46) To an ice-cold solution of 1 347 g of **45** (1 77 mmol) in 15 ml of THF was added 3.80 ml of a 0 5 M TBAF/THF solution (1.90 mmol) The yellow solution was stirred at ambient temperature for 90 minutes and then diluted with 50 ml of ether The organic layer was washed with water (15 ml) and brine (15 ml), dried ($MgSO_4$) and concentrated *in vacuo* Chromatography (Hex/EA 1/2) of the residue yielded 835 mg of **46** (1 60 mmol, 90 %) as a white foam, $[\alpha]_D$ -74.0° (c 1 1, CH_2Cl_2), **IR** ($CHCl_3$) 3420 (br), 3000 (m), 2945 (m), 1732 (s), 1688 (s), 1631 (s), 1410 (s), 1352 (s), 1170 (s), 690 (s); **^{1}H-NMR** (C_7D_8, 90 °C, 250 MHz, assignment with double resonance experiments) 1 54 (ddd, *J* 14 2, *J* 9 2, *J* 4 6, 1H, H_{4eq}), 1 76 (ddd, *J* 14 2, *J* 10 5, *J* 5 0, 1H, H_{4ax}), 1 83 (dd, *J* 13 5, *J* 8 9, 1H, H_{27}), 1 98 (ddd, *J* 11 6, *J* 4 6, 1H, H_5), 2 28 (m, 1H, $H_{27'}$), 2 39 (dd, *J* 14 8, *J* 6 4, 1H, H_{7eq}), 2 67 (dd, *J* 14 9, *J* 11 0, 1H, H_{7ax}), 2.83 (ddd, *J* 11 5, *J* 6 4, 1H, H_6), 2 95 (ddd, *J* 12 8, *J* 5 5, *J* 4 4, 1H, H_{3eq}), 3 19 (ddd, *J* 12 8, *J* 10 3, *J* 5 0, 1H, H_{3ax}), 3 45 (s, 3H, OCH_3), 3 90 (m, 1H, H_{25}), 4 06 (m, 1H, $H_{25'}$), 4 21 (m, 1H, H_{26}), 4 35 (d, *J* 14 4, 1H, NCHH'Ph), 4 75 (d, *J* 14 4, 1H, NCHH'Ph), 5 23 (AB, *J* 12 5, 2H, OCH_2Ph), 5 24 (s, 1H, H_9), 7 30 (m, 10H, Ar).

Methyl (4a*S*, 5*R*, 7a*R*, 10a*R*, 11a*S*)-2-benzyl-2,3,4,4a,5,6,7,7a,7b,10,10a,11-dodecahydro-7,7-(ethylenedioxy)-1-oxo-oxazolo[3,4-*j*]pyrrolo[2,3-*i*]isoquinoline-5-carboxylate (47) A solution of 200 0 mg of **46** (0 38 mmol), 10.0 mg of *p*-toluenesulfonic acid monohydrate (0 05 mmol) and 0 5 ml of freshly distilled ethylene glycol (18 mmol) in 30 ml of toluene was refluxed for 24 hours via a Dean-Stark trap, filled with molsieves 4Å (at regular intervals fresh ethylene glycol was added to the reaction!) After diluting with 20 ml of ether, the reaction mixture was washed with saturated $NaHCO_3$ solution (5 ml) and brine (5 ml), dried ($MgSO_4$) and concentrated *in vacuo* Chromatography (Hex/EA 1/2) of the residue yielded (in order of elution) 61 1 mg of recovered **46** (0 12 mmol) and 41 0 mg of **47** (0 09 mmol, 24 %, corrected yield 35 %) Crystallisation from toluene yielded **47** as colourless prisms, m p 99-100°C, **IR** ($CHCl_3$) 1762 (s), 1730 (s), 1628 (s), 690 (s), **^{1}H-NMR** (C_7D_8, 90 °C, 250 MHz, assignment with COSY) 1 73 (dd, *J* 12 0, *J* 5 1, 1H, H_{27}), 1 79 (m, 2H, H_{4eq} and H_{4ax}), 2 00 (dd, *J* 12 0, *J* 9 7, 1H, $H_{27'}$), 2 06 (ddd, *J* 13 2, *J* 4.8, *J* 1 5, 1H, H_{7eq}), 2 18 (dd, *J* 13 2, *J* 11 5, 1H, H_{7ax}), 2 24 (ddd, *J* 11 9, *J* 3 8, 1H, H_5), 2 90 (ddd, *J* 12 5, *J* 5 1, *J* 2 5, 1H, H_{3eq}), 3 11 (ddd, *J* 11 7, *J* 4 7, 1H, H_6), 3 43 (ddd, *J* 12 5, *J* 11 0, *J* 6 1, 1H, H_{3ax}), 3 58 (s, 3H, OCH_3), 3 74-4 07 (m, 6H, H_{25}, H_{26} and OCH_2CH_2O), 4 47 (d, *J* 14 5, 1H, NCHH'Ph), 4 54 (dd, *J* 13 1, *J* 6 8, 1H, $H_{25'}$), 4 74 (d, *J* 14 5, 1H, NCHH'Ph), 4 88 (d, *J* 1 4, 1H, H_9), 7 30 (m, 5H, Ar), MS (FD) 456 (M^+)

Acknowledgements

This investigation was carried out under auspicies of the Netherlands Foundation for Chemical Research (SON) with financial aid of the Netherlands Organization for Scientific Research (NWO) Helpful discussions with Dr H Hiemstra of this laboratory are gratefully acknowledged.

References and notes

1 Taken from the doctorate thesis of K M.J Brands, University of Amsterdam, 1990

2 (a) Sakai, R , Higa, T , Jefford, C W , Bernardinelli, G *J Am Chem Soc* , **1986**, *108*, 6404 (b) Sakai, R , Kohmoto, S , Higa, T , Jefford, C W , Bernardinelli, G *Tetrahedron Lett* , **1987**, *28*, 5493 (c) Ichiba, T , Sakai, R , Kohmoto, S , Saucy, G , Higa, T *ibid*, **1988**, *29*, 3083

3 Nakamura, H , Deng, S , Kobayashi, J , Okimuzi, Y , Tomotake, Y , Matsuzaki, T , Hirata, Y *Tetrahedron Lett* , **1987**, *28* 621

4 Brands, K M.J , Pandit, U K *Tetrahedron Lett* , **1989**, *30*, 1423

5 Hart, D J , McKinney, J A *Tetrahedron Lett* , **1989**, *30*, 2611

6 de Oliveira Imbroisi, D , Simpkins, N S *Tetrahedron Lett* , **1989**, *30*, 4309

7 (a) Nakagawa, M , Lai, Z , Torisawa, Y , Hino, T *Heterocycles*, **1990**, *31*, 999 (b) Torisawa, Y , Nakagawa, M., Arai, H , Lai, Z , Hino, T , Nakata, T ; Oishi, T *Tetrahedron Lett* , **1990**, *31*, 3195

8 Torisawa, Y , Hashimoto, A ; Nakagawa, M , Hino, T *Tetrahedron Lett* , **1989**, *30*, 6549

9 For a preliminary account Brands, K M.J , Pandit, U K *Heterocycles*, **1990**, *30*, 257

10 Throughout this paper manzamine A numbering is used, as introduced in reference 3

11 Recent reviews (a) Brieger, G , Bennett, J *Chem Rev* , **1980**, *80*, 63 (b) Desimoni, G , Tacconi, G , Barco, A , Pollini, G P , *Natural Products Synthesis Through Pericyclic Reactions*; ACS Monograph 180, Washington DC, 1983, p 164-191 (c) Taber, D F , *Intramolecular Diels-Alder Reactions and Alder Ene Reactions*; Springer Verlag New York, 1984 (d) Ciganek, E *Org React* , **1984**, *32*, 1 (e) Fallis, A G *Can J Chem* , **1984**, *62*, 183 (f) Craig, D *Chem Soc Rev* , **1987**, *16*, 187

12 Terminology as introduced in reference 11d.

13 The application of a Z-diene as a stereocontrol element in intramolecular Diels-Alder reactions is precedented. (a) House, H.O , Cronin, T H *J Org Chem* , **1965**, *30*, 1061 (b) Oppolzer, W , Fehr, C , Warnecke, J *Helv Chim Acta*, **1977**, *60*, 48 (c) Boeckman Jr , R K , Alessi, T R *J Am Chem Soc* , **1982**, *104*, 3216 (d) Pyne, S G , Pensel, M J , Fuchs, P L *ibid* , **1982**, *104*, 5719 (e) Hwang, G , Magnus, P *J Chem Soc Chem Comm* , **1983**, 693 (f) Koreeda, M , Luengo, J I *J Org Chem* , **1984**, *49*, 2080 (g) Yoshioka, M , Nakai, H , Ohno, M *J Am Chem Soc* , **1984**, *106*, 1133 (h) Wattanasin, S , Kathawala, F G , Boeckman Jr , R K *J Org Chem* , **1985**, *50*, 3810 (i) Hensel, M J , Palmer, J T , Learn, K S , Fuchs, P L *Synth Comm* , **1986**, *11*, 1297 (j) Palmer, J T , Learn, K S , Fuchs, P L *ibid* , **1986**, *11*, 1315 (k) Koreeda, M , Ricca, D J , Luengo, J I *J Org Chem* , **1988**, *53*, 5586 (l) Cooper, J A , Cornwall, P , Dell, C P , Knight, D W *Tetrahedron Lett* , **1988**, *29*, 2107

14 (a) Oppolzer, W , Fehr, C , Warnecke, J *Helv Chim Acta*, **1977**, *60*, 48 (b) Borch, R F , Evans, A J , Wade, J J *J Am Chem Soc* , **1977**, *99*, 1612 (c) Wilson, S R , Misra, R N *J Org Chem.*, **1980**, *45*, 5079 (d) Martin, S F , Williamson, S A , Gist, R P , Smith, K M *ibid* , **1983**, *48*, 5170 (e) Nantz, M H , Fuchs, P.L *ibid* , **1987**, *52*, 5298

15 (a) Masamune,S , Kamata, S , Schilling, W *J Am Chem Soc* , **1975**, *97*, 3515 (b) Masamune,S , Hayase, Y , Schilling, W , Chan, W K , Bates, G S *ibid* , **1977**, *99*, 6756

16 (a) Booth, P M , Fox, C M J , Ley, S V *J Chem Soc Perkin Tr I*, **1987**, 121 (b) Ley, S V , Woodward, P R *Tetrahedron Lett* , **1987**, *28*, 3019 (c) Ley, S V , Smith, S C , Woodward, P R *ibid* , **1988**, *29*, 5829 (d) Booth, P M ; Broughton H B , Ford, M J , Fox, C M J , Ley, S V , Slawin, A M Z , Williams, D J , Woodward, P R *Tetrahedron*, **1989**, *45*, 7565

17 Kim, H -O , Olsen, R K , Choi, O -S *J Org Chem* , **1987**, *52*, 4531

18 Coppola, G M , Schuster, M F , *Asymmetric Synthesis Construction of Chiral Molecules using Amino Acids*, Wiley New York, 1987

19 Hassell, C H , Thomas, J O *J Chem Soc C*, **1968**, 1495

20 Golebiowski, A , Jurczak, J *J Chem Soc Chem Comm* , **1989**, 263

21 Hwang, D -R , Helquist, P , Shekhani, M S *J Org Chem* , **1985**, *50*, 1264

22 Garner, P , Park, J M *J Org Chem* , **1987**, *52*, 2361

23 (a) Kollonitsch, J, Fuchs, O, Gabor, V *Nature*, **1954**, *173*, 125 (b) Kollonitsch, J, Fuchs, O, Gabor, V *ibid* , **1955**, *175*, 346 (c) Luly, J.R , Dellaria, J F , Plattner, J J , Soderquist, J L , Yi, N *J Org Chem.*, **1987**, *52*, 1487

24 Garegg, P.J , Samuelsson, B *J Chem. Soc Perkin Trans I*, **1980**, 2866

25 The method was not attested by examining the racemic product under identical conditions

26 (a) Fukuyama, T , Laird, A.A *Tetrahedron Lett* , **1986**, *27*, 6173 (b) Fukuyama, T , Li, L , Laird, A A , Frank, R K *J Am Chem Soc* , **1987**, *109*, 1587

27 Still, W C , Kahn, M , Mitra, A *J Org Chem* , **1978**, *43*, 2923

28 Danishefsky, S , Kitahara, T ; McKee, R , Schuda, P.F *J Am Chem Soc* , **1976**, *98*, 6715

29 (a) Schreiber, J , Maag, H , Hashimoto, N , Eschenmoser, E *Ang Chem* , **1971**, *83*, 330 (b) Bryson, T A , Bonitz, G H , Reichel, C J , Dardis, R E *J Org Chem* , **1980**, *45*, 524

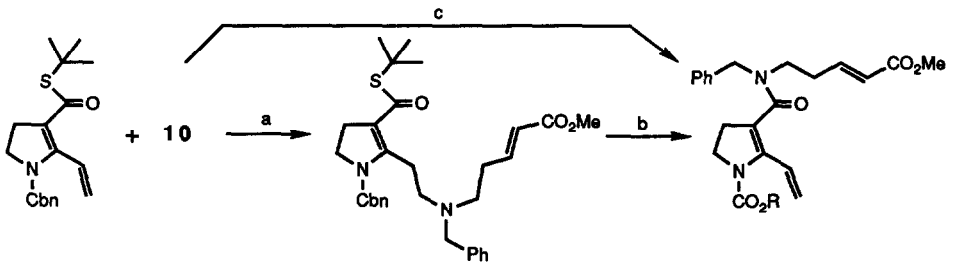
30 We are obliged to Prof B L Feringa of the University of Groningen, for pointing this possibility out to us Further studies on the generality of the dimethylaminomethylation procedure will also address the mechanism of the reaction

31 Some representative examples (a) Danishefsky, S , Guingant, A , Prisbylla, M *Tetrahedron Lett* , **1980**, *21*, 2033 (b) Shono, T , Matsumura, Y , Tsubata, K *J Am Chem Soc* , **1981**, *103*, 1172 (c) Hiemstra, H , Vijn, R.J , Speckamp, W N *J Org Chem* , **1988**, *53*, 3882 (d) Mooiweer, H H , Ettema, K W A , Hiemstra, H., Speckamp, W N *Tetrahedron*, **1990**, *46*, 2991

32 Ben-Ishai, D , Berger, A. *J Org Chem* , **1952**, *17*, 1564

33 Fleming,I , Goldhill, J , Patterson, I *Tetrahedron Lett* , **1979**, *20*, 3209

34 The following results were obtained in a model study phase Experimental details are given reference 1



(a) DIPEA, MeCN, RT,1h, 98 % (b) AgOTf, DIPEA, MeCN, RT, 4h, 82 % (c) AgOTf, DIPEA, MeCN, RT, 16h, 77 %

35 The catalytic stoichiometric dioxyosmylation procedure described by VanRheenen et. al. (ref 36), did not result in any conversion of the enecarbamate However, the procedure of Matteson (ref 37) did provide the requisite ketone after dehydration, but the yield was lower and the reaction was not amenable to larger scales

36 (a) VanRheenen, V , Kelly, R C , Cha, D F *Tetrahedron Lett* , **1976**, 1973 (b) VanRheenen, V , Cha, D F , Hartley, W N *Org Synth* , Coll Vol **VI**, 342

37 Ray, R , Matteson, D S *Tetrahedron Lett* , **1980**, *21*, 449

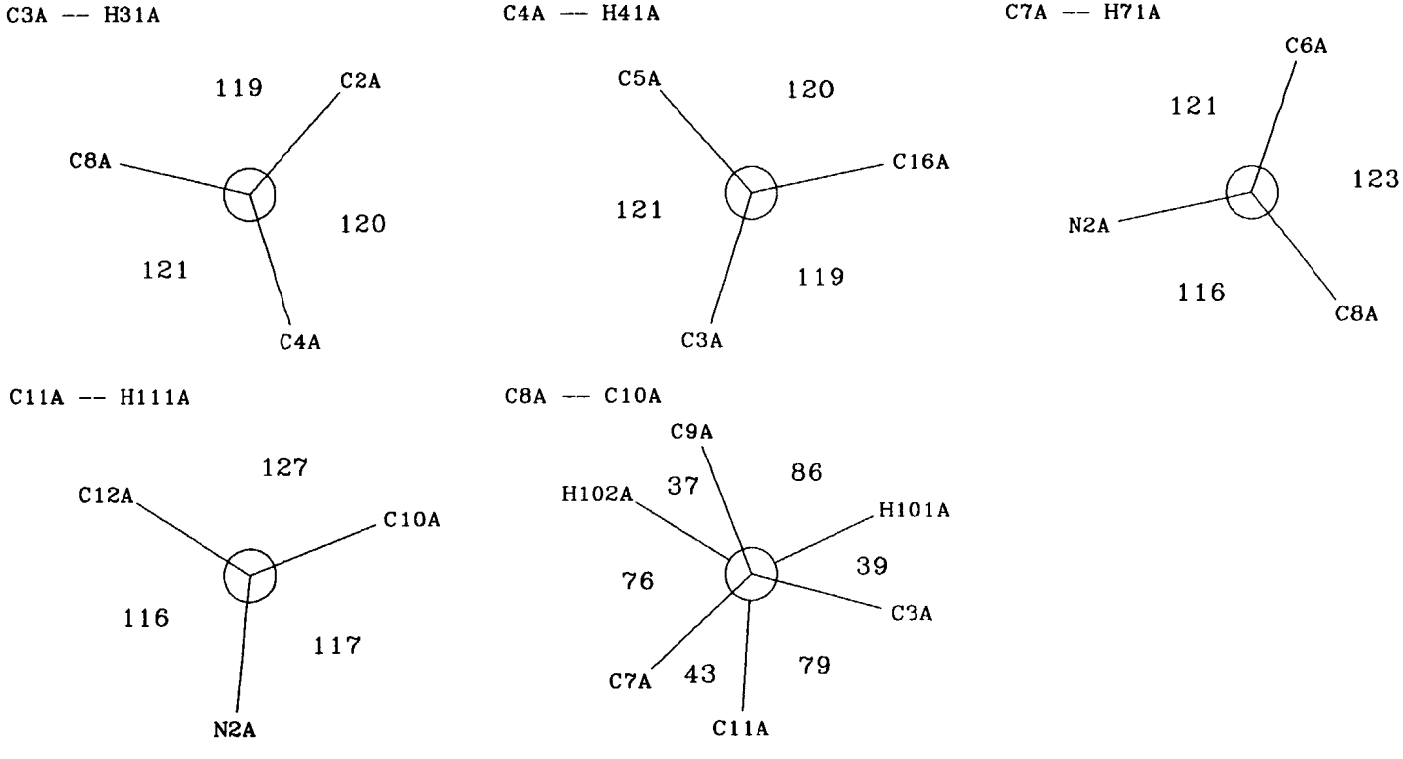
38 We wish to express our thanks to Dr R A.J Driessen of the Laboratory of Crystallography of the University of Amsterdam for the X-ray structure of **47** Details are to be published elsewhere

39 IUPAC, *Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F and H (1979 edition)*; Pergamon Press Oxford, 1979

40 Winkle, M R , Lansinger, J M , Ronald, R C *J Chem Soc Chem Comm* , **1980**, 87

Synthesis of the homochiral "tricyclic heart" of manzamine A

by Karel M.J. Brands, Arthur A.P. Meekel and Upendra K. Pandit
Laboratory for Organic Chemistry, University of Amsterdam,
Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands.



Synthesis of the homochiral "tricyclic heart" of manzamine A

by Karel M.J. Brands, Arthur A.P. Meekel and Upendra K. Pandit
Laboratory for Organic Chemistry, University of Amsterdam,
Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands.