Enantioselective Synthesis of an Allenyl Derivative of Pipecolic Acid

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Received May 4, 1998

Keywords: Iminium ion / Propargylsilane / Pipecolic acid derivative / Amino acids / Asymmetric synthesis

Addition of a propargylsilane moiety onto chiral cyclic iminium ions occurs with a high level of stereoselectivity intermolecularly as well as intramolecularly. This operation generates allenic α-amino acids precursors. An isomerization leading to a 1,3-dienyl compound precludes the formation of an allenic amino acid in the acyclic series; however, this isomerization did not take place with the cyclic α-amino ester which was thus obtained with a 55 % ee. AM1 calculations explain the difference of reactivity between cyclic and acyclic compounds on a conformational basis.

Introduction

Unsaturated α-amino acids are interesting targets owing to their potential biological activity.[1] Introduction of α-vinyl or α-ethynyl substituents can change the properties of certain amino acids, and transform them into irreversible inhibitors with therapeutic applications.[2] In particular, an allenyl substituent may act as an electrophilic acceptor, thus allowing α-allenic amino acids to appear as attractive candidates for enzyme inhibitors. For example, γ-allenyl GABA[3] and α-allenyl DOPA[4] were shown to be potent enzyme-activated irreversible inhibitors of GABA transaminase and bacterial aromatic group amino acid decarboxylase, respectively.

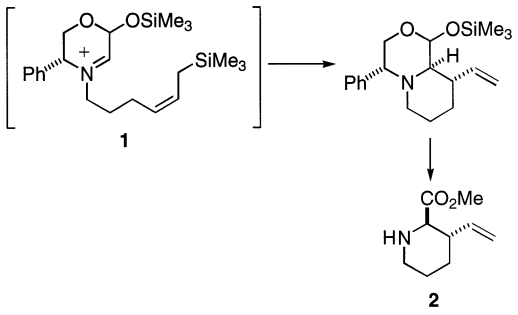
The well-known instability of the allenyl moiety accounts for the scarceness of reported preparation of β-allenyl[5] and γ-allenyl[6] amino acids and this is specially clear in the field of asymmetric synthesis: to our knowledge, no *N*-unprotected β-allenyl α-amino acid was ever synthesized in optically active form. We wish to present a methodology which provides access to such compounds as derivatives of pipecolic acid. As it will be shown below, an allenyl/1,3-dienyl isomerization can take place and this is an obvious obstacle in the way of a stereoselective synthesis which adds further to the already reported difficulties.[5]

Results and Discussion

We have recently shown[7] that α-vinylpipecolic acid methyl ester (**2**) can be synthesized (see Scheme 1) by an intramolecular addition of an allylsilane moiety onto a transient iminium ion **1**.

On this basis, it can be anticipated that the use of a propargylsilane substituent should allow the formation of an allenic derivative as shown on Scheme 2 which outlines the corresponding retrosynthetic analysis. The target molecule **3** can be traced to bicyclic compound **4**. This molecule is

Scheme 1



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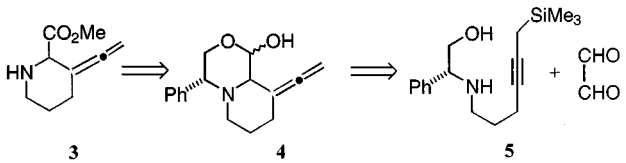
the result of the expected cyclization of a transient iminium ion similar to **1** with the propargylsilane terminator.

Scheme 2



3 4 5

In order to test the feasibility of this process, we first planned to prepare an acyclic allenic amino acid. Thus (*R*)-*N*-methylphenylglycinol **6** was treated with glyoxal in the presence of thiophenol (see Scheme 3), following a published procedure.[8] The produced morpholinic hemiketal **7** was protected as its *tert*-butyldimethylsilyl derivative **8** which was then treated with trimethylpropargylsilane in order to yield adduct **9**. Fluoride ion mediated desilylation followed by a Swern oxidation transformed compound **9** into lactone **10**. This allenic derivative was obtained as a diastereomerically pure compound. On the basis of our previous works[9] an (*R*) absolute configuration at the newly created stereocenter is highly probable.

It appears therefore that the anticipated reaction is realizable. However, the deprotection of the α-amino acid did not

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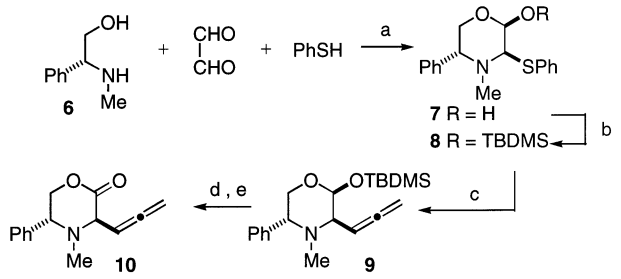
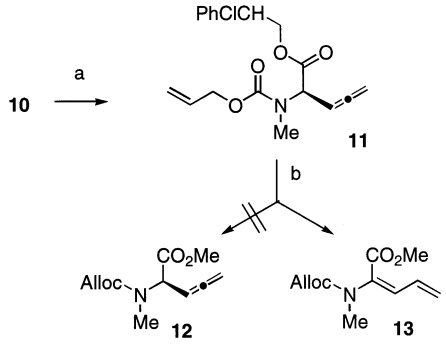
Scheme 3. Reagents and conditions: (a) room temp., 3 h, 85%; (b) TBDMSCl, imidazole, room temp., 12 h, 84%; (c) $ZnBr_2$, propargylsilane, THF, room temp., 18 h; (d) nBu_4NF, THF, 0°C, 30 min., 70% from **8**; $(COCl)_2$, DMSO, CH_2Cl_2, NEt_3, −50°C, 1 h, 75%



lead to an allenic compound but to another amino acid: the 1,3-dienyl isomer. As shown in Scheme 4, debenzylation of compound **10** (via the carbamate **11**) and final methanolysis afforded the 1,3-dienic amino acid methyl ester **13**.

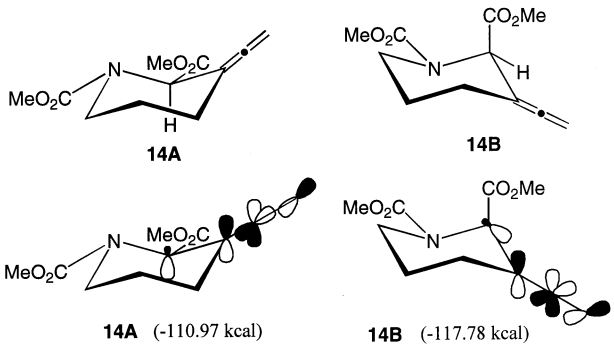
Scheme 4. Reagents and conditions: (a) allyl chloroformate, CH_3CN, reflux, 3 d, 65%; KCN, MeOH, 60°C, 3 h, 65%



We assumed that this undesirable isomerization would not occur in the case of a cyclic amino acid. AM1 calculations were performed on conformations **A** and **B** of a cyclic analogue of the allenyl derivative **12**, i.e. model compound **14**. These calculations showed that conformation **B** was the more stable (see Figure 1). The axial geometry of the ester group in the favored conformation **B** can be explained by an alkyl 2-ketone related effect.[10] In this structure, the π* orbital of the exocyclic double bond cannot overlap with the σ C−H orbital in the α position. Since this overlap, which is responsible for the allenyl/1,3-dienyl isomerization, is prevented in a cyclic framework, it was predicted that the production of allenic amino acid should be easier in this case. On the other hand, the σ−π* overlap which is responsible for the allenyl/1,3-dienyl isomerization can be easily attained in the acyclic compound **12**, thus explaining the formation of the thermodynamically favored 1,3-dienyl isomeric compound **13**.

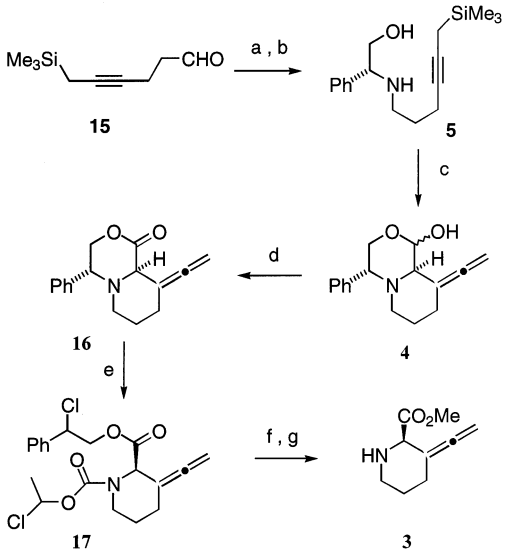
The synthesis (see Scheme 5) of the allenic pipecolic acid methyl ester commences with the reaction of the known[11] aldehyde **15** with (*R*)-phenylglycinol. The intermediate oxazolidine was reduced in situ with $NaBH_4$ in order to afford amino alcohol **5**. Treatment of the latter compound with an

Figure 1. Calculated conformations of allenic compound **14**



aqueous solution of glyoxal yielded bicyclic hemiketal **4** which was submitted to a Swern oxidation.

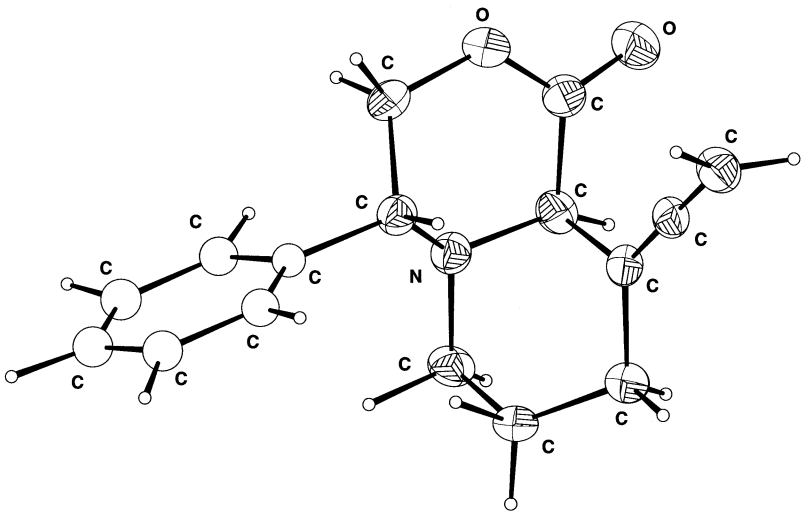
Scheme 5. Reagents and conditions: (*R*)-2-phenylglycinol, CH_2Cl_2, room temp., 30 min; (b) $NaBH_4$, EtOH, 0°C to room temp., 15 min, 70% from **15**; (c) CHOCHO, THF/H_2O, 1:1, room temp., 3 d; (d) $(COCl)_2$, DMSO, CH_2Cl_2, NEt_3, −50°C, 1 h, 80%; (e) $CH_3CHClCOCl$, 4-A molecular sieves, $(CH_2Cl)_2$, 80°C, 24 h, 80%; (f) KCN, MeOH, room temp., 3 h; (g) MeOH, reflux, 4 h, 50% from **16**



Lactone **16** was obtained in a diastereomerically pure form and an X-ray crystallographic analysis of this compound (Figure 2) showed a *cis* relationship between the hydrogen atom at the ring junction and the phenyl group, thus establishing an (*R*) absolute configuration at the ring junction.

Treatment of lactone **16** with 1-chloroethyl chloroformate[12] effected the required *N*-debenzylation and yielded compound **17**. A simple and straightforward transformation was then effected: (i) transesterification with KCN/MeOH,[13] and (ii) elimination of the carbamate moiety by heating in methanol to give the β-allenic α-amino ester **3**. This deprotection sequence was selected because it required only very mild experimental conditions which are compatible with the allenyl moiety. In this respect, attempts with either vinyl chloroformate,[14a] 2-(trimethylsilyl)ethyl

Figure 2. Crystallographic analysis of lactone **16**



chloroformate,[14b] or allyl chloroformate[14c] as alternative classical debenzylation methods were unsatisfactory.

Chiral HPLC analysis was performed on the eventually produced amino acid derivative **3** and this measure was checked by comparison with the racemate. Enantiomeric excess of the allenic α-amino acid methyl ester amounts to 55%. Partial racemization therefore occurred in this case without rearrangement to the more stable diene system. This fact can be ascribed to a kinetically controlled protonation of the carbanion derived from allenic ester **3**. AM1 calculations show that in such an enolate the fractional negative charge developed at C-2 (−0.40 instead of +0.03 in compound **3**) is much more pronounced than the corresponding one developed at the central allenic carbon atom (−0.26 instead of −0.15 in compound **3**).

Albeit modest, this 55% enantiomeric excess demonstrates that the asymmetric synthesis of β-allenic α-amino acids is realizable in the cyclic series. As shown above, a similar approach in the acyclic series is plagued with the allenyl/1,3-dienyl isomerization which is favored in this case by a higher degree of rotational freedom.

We thank Dr. *J. Vaissermann* (Université P. et M. Curie, Paris) who performed the crystallographical analysis and Mr. *A. Valleix* (CEA, Saclay) for the HPLC determination of the enantiomeric excess.

Experimental Section

General Comments: ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$ solution) were recorded with a Brucker ARX 250 spectrometer at 250 and 62.5 MHz, respectively; chemical shifts are reported in ppm from TMS. − Optical rotations were determined with a Perkin-Elmer 141 instrument. − IR spectra were recorded with a Mattson 1000 FTIR spectrometer (characteristic absorptions are given in cm^{-1}). − All reactions were carried out under nitrogen except those performed in aqueous medium. THF was distilled from sodium/benzophenone ketyl, dichloromethane and dichloroethane from CaH_2 before use. − Column chromatography was performed on silica gel, 230−400 mesh by using various mixtures of diethyl ether (E) and petroleum ether (EP). − HRMS was measured in the EI mode with an ionization potential of 70 eV; the accurate measurements were done with a resolving power of 10,000. − Melting points are uncorrected.

(2S,3R,5R)-2-(tert-Butyldimethylsilyloxy)-4-methyl-3-phenyl-5-propa-1,2-dienylmorpholine (**9**): Zinc bromide (2.2 g, 9.6 mmol) was added at room temp. to a solution of silylated derivative **8**[9] (2 g, 4.8 mmol) in THF (20 ml). After complete dissolution, propargylsilane (0.8 g, 7.2 mmol) was introduced. Stirring was continued for 18 h, and water was added. After extraction with ether, the organic layers were washed with a saturated ammonium sulfate solution and dried with $MgSO_4$. After concentration, compound **9** was obtained quantitatively as an orange oil which was used in the next step without further purification. − ^{1}H NMR: δ = 0.13 [s, 6 H, $Si(CH_3)_2$], 0.91 [s, 9 H, $C(CH_3)_3$], 2.07(s, 3 H, NCH_3), 3.39−3.57 (m, 3 H, NCH, NCHPh and OC*H*H), 3.73−3.82 (m, 1 H, OCH*H*) 4.68 (d, *J* = 7 Hz, 2 H, C=CH_2), 5.08 (d, *J* = 2 Hz, 1 H, OCHO), 5.37−5.48 (m, 1 H, C*H*=C=CH_2), 7.27−7.30 (m, 5 H, Ph). − ^{13}C NMR: δ = −2.5 and −1.5 [$Si(CH_3)_2$], 18.1 [*C*$(CH_3)_3$], 25.7 [C(*C*$H_3)_3$], 40.0 (NCH_3), 61.0 (N*C*HPh), 66.0 (NCH), 71.6 (CH_2O), 73.7 (C=*C*H_2), 81.4 (*C*H=C=CH_2), 96.2 (OCHO), 127.8, 128.4, 128.6, 138.9 (Ph), 210.8 (CH=*C*=CH_2).

(3R,5R)-4-Methyl-5-phenyl-3-(propa-1,2-dienyl)morpholin-2-one (**10**): A 1 M solution of tetrabutylammonium fluoride in THF (5.3 ml) was added dropwise to a solution of crude compound **9** (4.8 mmol) in THF (50 ml) at 0°C. After stirring for 30 min at this temperature, the reaction mixture was quenched by adding water. Extraction with ether was followed by drying the organic layers with $MgSO_4$ and concentration. The residue was then chromatographed (E/EP, 30:70) to afford the intermediate lactol (0.77 g, 3.3 mmol, 70% from **8**) which was oxidized directly. Dimethyl sulfoxide (0.70 ml, 9.9 mmol) was added dropwise to oxalyl chloride (0.43 ml, 4.9 mmol) in dichloromethane (8.3 ml) at −50°C. After 1 h at this temperature, triethylamine (2.3 ml, 16.5 mmol) was introduced, and the mixture was allowed to warm to room temp. The residue was diluted with water and extracted with dichloromethane. The organic extracts were washed with water, dried with $MgSO_4$, and concentrated in vacuo. Chromatography (E/EP, 30:70) afforded lactone **10** as a diastereoisomerically pure solid (0.57 g, 75%), m.p. 60°C. − $[\alpha]_D^{20}$ = −189 (*c* = 0.8, $HCCl_3$). − ^{1}H NMR: δ = 2.11

(s, 3 H, NCH_3), 3.93 (dd, J = 5 and 9 Hz, 1 H, NCHPh), 4.23−4.39 (m, 3 H, CH_2O and NCHCO), 4.87 (d, J = 2 Hz, 1 H, CH=C=CH*H*), 4.90 (dd, J = 1 and 2 Hz, 1 H, CH=C=C*H*H), 5.31−5.39 (m, 1 H, C*H*=C=CH_2), 7.24−7.33 (m, 5 H, Ph). − ^{13}C NMR: δ = 37.2 (NCH_3), 57.4 (NCHPh), 62.8 (NCHCO), 72.1 (CH_2O), 76.2 (CH=C=*C*H_2), 82.3 (*C*H=C=CH_2), 127.3, 127.6, 127.8, 135.6 (Ph), 167.3 (C=O), 208.5 (CH=*C*=CH_2).

Carbamate Derivative **11**: Allyl chloroformate (0.56 ml, 5.28 mmol) was added to a solution of lactone **10** (0.24 g, 1.05 mmol) in acetonitrile (7 ml). This mixture was refluxed for 3 d and the solvent was evaporated. The residue was chromatographed on silica gel (E/EP, 15:85) to give compound **11** as an oil (0.24 g, 65%). − ^{1}H NMR: δ = 2.90 (s, 3 H, NCH_3), 4.48−4.57 (m, 2 H, CH_2O), 4.59−4.66 (m, 2 H, NCO_2CH_2), 4.87−4.92 (m, 2 H, CH=C=C*H*$_2$), 5.09 (dd, J = 6 and 7 Hz, 1 H, NCHPh), 5.20−5.45 (m, 4 H, NCH, CH*H*O and CH_2CH=C*H*$_2$), 5.83−6.01 (m, 1 H, C*H*HO), 7.34−7.44 (m, 5 H, Ph). − ^{13}C NMR: δ = 32.0 (NCH_3), 58.7 (NCH), 59.6 (CHPh), 66.8 (NCO_2CH_2), 68.9 (CH_2O), 78.6 (CH=C=*C*H_2), 86.2 (*C*H=C=CH_2), 117.8 (CH_2CH=*C*H_2), 127.8, 129.2, 129.4, 137.7, (Ph), 133.1 (CH_2*C*H=CH_2), 156.8 (NCO_2), 169.7 (CO_2), 209.4 (CH=*C*=CH_2).

1,2-Dienyl Derivative **13**: Potassium cyanide (0.04 g, 0.55 mmol) was added to a solution of carbamate **11** (0.13 g, 0.37 mmol) in MeOH (1.8 ml). The mixture was heated at 60°C for 3 h and the solvent was evaporated under reduced pressure. The residue was chromatographed (E/EP, 25:75) to furnish compound **13** (0.05 g, 65%) as a colourless oil. − ^{1}H NMR: δ = 3.01 (s, 3 H, NCH_3), 3.72 (s, 3 H, CO_2CH_3), 4.47−4.51 (m, 2 H, CH_2O), 5.06−5.18 (m, 2 H, CH_2CH=C*H*$_2$), 5.49−5.88 (m, 3 H, CH_2C*H*=CH_2 and C=CHCH=C*H*$_2$), 6.39−6.60 (m, 1 H, C=CHC*H*=CH_2), 7.06 (d, J = 11 Hz, 1 H, C=C*H*CH=CH_2). − ^{13}C NMR: 36.1 (NCH_3), 51.6 (CO_2*C*H_3), 65.6 (CH_2O), 116.4 (CH_2CH=*C*H_2), 126.2 (C=CHCH=*C*H_2), 129.6 (CH_2*C*H=CH_2), 131.8 (C=CH*C*H=CH_2), 136.4 (C=*C*HCH=CH_2), 154.9 (NCO_2), 164.4 (*C*O_2CH_3).

AM1 Calculations: The geometries and energies of molecules **14A** and **14B** were calculated using the AM1[15] Hamiltonian in the AMPAC version 4.0 QCPE No 527. They were obtained by using the Davidson-Fletcher-Powell algorithm (FLEPO procedure) that minimizes the energy with respect to all internal coordinates.

(2R)-2-Phenyl-2-(6-trimethylsilanylhex-4-ynylamino)ethanol (**5**): The known[13] aldehyde **15** (3 g, 17.7 mmol) was dissolved in CH_2Cl_2 (50 ml) and (2*R*)-2-phenylglycinol (2.5 g, 18.2 mmol) was added as a solid at room temp. Stirring was maintained for 30 min and the solvent was evaporated under reduced pressure to give quantitatively the oxazolidines as a mixture (40:60) of two diastereoisomers. Absolute ethanol (40 ml) was added to this residue and the resultant solution was treated at 0°C with a solution of sodium tetrahydroborate (0.67 mg, 17.7 mmol) in absolute ethanol (50 ml). After the end of addition, the mixture was stirred for 15 min at room temp. and ethanol was evaporated. The crude residue dissolved in ether was washed with brine and dried with $MgSO_4$. Chromatography (E/EP, 60:40) furnished compound **5** as a colourless oil (4 g, 70%). − $[\alpha]_D^{20}$ = −62 (*c* = 1.2, $HCCl_3$). − ^{1}H NMR: δ = 0.07 [s, 9 H, $Si(CH_3)_3$], 1.40 (t, J = 3 Hz, 2 H, CH_2Si), 1.62−1.69 (m, 2 H, CH_2C*H*$_2$CH$_2$), 2.19−2.24 (m, 2 H, C*H*$_2$C≡CCH$_2$Si), 2.55−2.62 (m, 1 H, NC*H*H), 2.64−2.71 (m, 1 H, NCH*H*), 3.53 (dd, J = 8 and 10 Hz, 1 H, C*H*HO), 3.72 (dd, J = 4 and 10 Hz, 1 H, CH*H*O), 3.77 (dd, J = 4 and 8 Hz, 1 H, NCHPh), 7.26−7.38 (m, 5 H, Ph). − ^{13}C NMR: δ = 0.0 [$Si(CH_3)_3$], 8.9 (CH_2Si), 18.9 (*C*H_2C≡C*C*H_2Si), 31.9 (CH_2*C*H_2CH$_2$), 48.5 (NCH_2), 66.6 (NCHPh), 68.7 (CH_2O), 80.0 and 80.2 (C≡C), 129.2, 129.6, 130.7, 142.9 (Ph). − $C_{17}H_{27}NOSi$ (289.4): calcd. C 70.53, H 9.40, N 4.84; found C 70.53, H 9.49, N 4.83.

(4R,8aR)-4-Phenyl-9-vinylideneoctahydropyrido[2,1-c][1,4]-oxazin-1-ol (**4**): To a mixture of silylated α-aminoalcohol **5** (1.5 g, 3.4 mmol) in THF/H_2O (14 ml, 1:1) was added an aqueous solution of glyoxal (1.4 ml, 9.4 mmol) at room temp. The resulting mixture was stirred for 3 d at room temp. and water and ether were added. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined ether extracts were washed with water and brine, dried ($MgSO_4$), and concentrated. Crude product **4** was obtained as an epimeric mixture (80:20) at the hemiacetalic carbon atom and was rapidly chromatographed (E/EP, 20:80) (0.9 g, 70%). ^{1}H- and ^{13}C-NMR spectra of this mixture of diastereoisomers gave the following characteristic peaks for the major isomer. − ^{1}H NMR: δ = 1.21−1.25 (m, 1 H, CH_2CH*H*CH$_2$), 1.76−1.90 (m, 1 H, CH_2CH*H*CH$_2$), 2.19−2.32 (m, 1 H,CH*H*C=), 2.46−2.50 (m, 1 H, C*H*HC=), 2.53−2.61 (m, 1 H, NC*H*H), 2.89−2.93 (m, 1 H, NCH*H*), 3.52−3.62 (m, 2 H, C*H*HO and NCHC=), 3.95 (t, J = 11 Hz, 1 H, C*H*HO), 4.19 (dd, J = 4 and 10 Hz, 1 H, NCHPh), 4.75−4.79 (m, 1 H, C=CH*H*), 4.89−4.94 (m, 1 H, C=C*H*H), 5.24 (s, 1 H, OCHO), 7.30−7.43 (m, 5 H, Ph). − ^{13}C NMR: δ = 19.7 (CH_2*C*H$_2$CH$_2$), 30.0 (*C*H_2C=C), 49.3 (NCH_2), 57.5 (N*C*HCO), 61.5 (NCHPh), 65.5 (CH_2O), 76.0 (C=C=*C*H_2), 94.6 (*C*=C=CH_2), 127.9, 128.4, 128.7, 138.1 (Ph), 203.6 (C=*C*=CH_2). − IR: 3505, 1974.

(4R,8aR)-4-Phenyl-9-vinylidenehexahydropyrido[2,1-c][1,4]-oxazin-1-one (**16**): Dimethyl sulfoxide (0.7 ml, 9.7 mmol) was added dropwise to a solution of oxalyl chloride (0.42 ml, 4.9 mmol) in CH_2Cl_2 at −50°C. After stirring for 10 min at this temperature, a solution of hemiacetal **4** (0.8 g, 3.2 mmol) in CH_2Cl_2 (7 ml) was added. After 1 h at −50°C, triethylamine (2.2 ml, 16.2 mmol) was slowly introduced and the mixture was allowed to warm to room temp. within 1.5 h. Quenching with water, extraction with CH_2Cl_2, drying of the combined organic layers ($MgSO_4$), and evaporation of the solvent was followed by purification of the residue by chromatography (E/EP, 50:50) to afford lactone **16** as a clear yellow solid (0.65 g, 80%), m.p. 107°C. − $[\alpha]_D^{20}$ = −186 (*c* = 0.9, $HCCl_3$). − ^{1}H NMR: δ = 1.32−1.40 (m, 1 H, CH_2CH*H*CH$_2$), 1.65−1.76 (m, 1 H, CH_2C*H*HCH$_2$), 2.26−2.35 (m, 1 H, C*H*HC=), 2.49−2.55 (m, 1 H, C*H*HC=), 2.68−2.83 (m, 2 H, NCH_2), 4.23−4.36 (m, 3 H, CH_2O and NCH), 4.54 (t, J = 3 Hz, 1 H, NCH), 4.88 (m, 2 H, =CH_2), 7.36−7.41 (m, 5 H, Ph). − ^{13}C NMR: δ = 22.5 (CH_2*C*H$_2$CH$_2$), 30.2 (*C*H_2C=), 50.0 (NCH_2), 58.4 (NCH), 64.7 (NCH), 74.3 (CH_2O), 78.3 (C=*C*H_2), 95.6 (*C*=C=CH_2), 129.5, 129.8, 130.2, 137.5 (Ph), 168.6 (CO), 204.5 (C=*C*=CH_2). − IR: 1965, 1747. − $C_{16}H_{17}NO_2$ (255.3): calcd. C 75.26, H 6.71, N 5.48; found C 75.14, H 6.71, N 5.54.

Crystal Data Collection for **16**[16] ($C_{16}H_{17}NO_2$): Data were collected at room temperature with an Enraf-Nonius CAD4 diffractometer. Accurate cell dimensions are a = 11.085(5), b = 11.131(5), c = 10.863(5) Å, V = 1340 Å^3. The unit cell is orthorhombic, non-centrosymmetric space group $P2_12_12_1$, Z = 4, D_c = 1.26 g cm^{-3}, μ(Mo-K_α) = 0.78 cm^{-1}. No significant variations were observed in the intensities of two checked reflections during data collection. The data were collected for Lorentz and polarization effects. The program used was CRYSTALQ. The structure was solved by use of *SHELXS86, Program for Crystal Structure Solution*, G. M. Sheldrick, University of Gottingen, **1986**, and refined by full-matrix least-squares analysis with anisotropic thermal parameters for all non-hydrogen atoms. H atom were introduced in calculated position in the last refinement. The final refinement

using 828 reflections [with $(F_o)^2 > 2\sigma(F_o)^2$] were used to solve and refine the structure to $R = 0.0535$ and $R_w = 0.0677$.

Carbamate **17**: 1-Chloroethyl chloroformate (0.9 ml, 8.3 mmol) was added to a solution of lactone **16** (0.25 g, 1 mmol) in 1,2-dichloroethane (0.9 ml) with 4-Å molecular sieves. The mixture was heated at 80°C for 24 h and the solvent was evaporated. The crude residue was filtered through silica gel (E/EP, 50:50) to afford carbamate **17** (0.34 g, 80%) as a complex mixture of four diastereoisomers. Only characteristic peaks in the ^{1}H- and ^{13}C-NMR spectra are given for the major isomer. – ^{1}H NMR: δ = 1.76 (d, J = 5.8 Hz, CH_3), 1.62–2.28 (m, 4 H, CH_2CH_2), 2.82–3.25 (m, 2 H, NC*H*H), 3.93–4.25 (m,1H NCH*H*), 4.34–4.58 (m, 2 H, CH_2O), 4.64–4.84 (m, 2 H, C=CH_2), 4.97–5.05 (m, 1 H, PhCHCl), 5.27 (s, 1 H, NCHCO), 6.49–6.53 (m, 1 H, OCHCl), 7.28–7.34 (m, 5 H, Ph). – ^{13}C NMR: δ = 25.4 and 25.9 (CH_2CH_2 and CH_3), 41.7 (NCH_2), 58.0 and 59.2 (PhCHCl and N*C*HCO), 68.4 (CH_2O), 76.2 (C=*C*H_2), 83.3 (OCHCl), 93.9 (*C*=C=CH_2), 127.5, 128.8, 129.0, 137.2 (Ph), 152.6 (OCON), 169.5 (O*C*OC), 205.9 (C=*C*=CH_2). – IR: 1974, 1757, 1733.

Methyl 3-Vinylidenepiperidine-2-carboxylate (**3**): Potassium cyanide (0.055 g, 0.85 mmol) was added to a solution of carbamate **17** (0.17 g, 0.43 mmol) in MeOH (3.5 ml). After stirring for 3 h at room temp., the reaction mixture was concentrated. The residue was dissolved in CH_2Cl_2, the resultant organic layer was washed with water and brine, dried, and concentrated. The crude product was directly treated with MeOH (4 ml) and the solution was heated at 80°C for 3 h. After cooling, the solvent was evaporated and chromatography (E/EP, 70:30, then Et_2O) afforded amino ester **3** as a thick oil (0.035 g, 50%). – $[\alpha]_D^{20} = -110$ (c = 0.9, $HCCl_3$). – ^{1}H NMR: δ = 1.46–1.67 (m, 2 H, $CH_2CH_2CH_2$), 2.11–2.34 (m, 3 H, CH_2C= and NH), 2.64–2.74 (m, 1 H, NC*H*H), 3.05 (td, J = 4.4 and 4.8 Hz, 1 H, NCH*H*), 3.65 (s, 3 H, CO_2CH_3), 3.99 (t, J = 2.3 Hz, 1 H, NCHCO), 4.62–4.64 (m, 2 H, C=CH_2). – ^{13}C NMR: δ = 27.3 (CH_2), 28.6 (CH_2), 44.2 (NCH_2), 51.7 (CH_3), 61.0 (N*C*HCO), 75.8 (C=CH_2), 98.2 (*C*=C=CH_2), 171.8 (CO), 202.4 (C=*C*=CH_2). – IR: 1974, 1757. – HRMS: calcd. for $C_9H_{14}NO_2$ 168.1025, found 168.1009.

Determination of the Enantiomeric Purity of Amino Ester **3**: HPLC was performed using an (R,R) Whelk O1 (250 × 4.6) column at 0°C. Flow: 0.6 ml/min. Eluent: hexane/ethanol/diethylamine, 99:1:0.05; UV detection.

[1] C. Walsh, *Tetrahedron* **1982**, *38*, 871–909; R. G. Shea, J. N. Fitzner, J. E. Fankhauser, A. Spaltenstein, P. A. Carpino, R. M. Peevey, D. V. Pratt, B. J. Tenge, P. B. Hopkins, *J. Org. Chem.* **1986**, *51*, 5243–5252; C. Angst, *Pure Appl. Chem.* **1987**, *59*, 373–380.

[2] G. Ribereau-Gayon, C. Danzin, M. G. Palfreyman, M. Aubry, J. Wagner, B. W. Metcalf, M. J. Jung, *J. Biochem. Pharmacol.* **1979**, *28*, 1331–1338.

[3] A. L. Castelhano, A. Krantz, *J. Am. Chem. Soc.* **1984**, *106*, 1877–1879.

[4] A. L. Castelhano, D. H Pliura, G. J. Taylor, K. C. Hsieh, A. Krantz, *J. Am. Chem. Soc.* **1984**, *106*, 2734–2735; P. Casara, K. Jund, P. Bey, *Tetrahedron Lett.* **1984**, *25*, 1891–1894.

[5] H.H. Mooiweer, H. Hiemstra, H.P. Fortgens, W.N. Speckamp, *Tetrahedron Lett.* **1987, 28**, 3285–3288; M. P. Doyle, V. Bagheri, E. E. Claxton, *J. Chem. Soc., Chem. Commun.* **1990**, 46–48; D. P. G. Hamon, R. A. Massy-Westropp, P. Razzino, *J. Chem. Soc., Chem. Commun.* **1991**, 722–724; D. P. G. Hamon, R. A. Massy-Westropp, P. Razzino, *Tetrahedron* **1995**, *51*, 4183–4194; U. Kazmaier, C. H. Gorbitz, *Synthesis* **1996**, 1489–1493; A. L. Castelhano, S. Horne, G. J. Taylor, R. Billedeau, A. Krantz, *Tetrahedron* **1988**, *44*, 5451–5466.

[6] J. E. Baldwin, R. M. Adlington, A. Basak, *J. Chem. Soc., Chem. Commun.* **1984**,1284–1285; M. J. Dunn, R. F. W. Jackson, *J. Chem. Soc., Chem. Commun.* **1992**, 319–320; M. J. Dunn, R. F. W. Jackson, J. Pietruszka, D. Turner, *J. Org. Chem.* **1995**, *60*, 2210–2215; B. Cazes, D. Djahanbini, J. Goré, J. P. Genêt, J. M. Gaudin, *Synthesis* **1988**, 983–985.

[7] C. Agami, D. Bihan, R. Morgentin, C. Puchot-Kadouri, *Synlett* **1997**, 799–800.

[8] C. Agami, F. Couty, B. Prince, C. Puchot, *Tetrahedron* **1991**, *47*, 4343–4354.

[9] C. Agami, D. Bihan, C. Kadouri-Puchot, *Tetrahedron* **1996**, *52*, 9079–9086; C. Agami, F. Couty, C. Puchot-Kadouri, *Synlett* **1998**, 449–456 and references cited therein.

[10] E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, 2nd ed., Wiley, **1994**, p. 733.

[11] W. J. Klaver, M. J.. Moolenaar, H. Hiemstra, W. N. Speckamp, *Tetrahedron* **1988**, *44*, 3805–3818.

[12] B. V. Yang, D. O.′Rourke, J. Li, *Synlett* **1993**, 195–196.

[13] K. Mori, M. Tominaga, T. Takigawa, M. Matsui, *Synthesis* **1973**, 790–791.

[14] M. Fieser, L.F. Fieser, *Reagents for Organic Synthesis*, Wiley, [14a] **1994**, vol. 17, p. 190; [14b] **1989**, vol. 14, p. 331; [14c] **1988**, vol. 13, p. 9.

[15] M. J. S. Dewar, F. G. Zoebisch, E. F. Healy, J. J. P. Stewart, *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.

[16] Crystallographic data for the structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no CCDC-101376. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk).

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