An Efficient Synthesis of Chiral Cyclic β-Amino Acids via Asymmetric Hydrogenation

Cyrille Pousset,*[a,b] Roland Callens,[b] Angela Marinetti,[a] Marc Larchevêque*[a]

[a] Laboratoire de Synthèse Organique associé au CNRS ENSCP, 11 rue Pierre et Marie Curie, 75231 Paris Cedex 05, France

[b] Peptisyntha et Cie S.N.C., 310 rue de Ransbeek, Bruxelles, Belgium
Fax +32(22)642225; E-mail: larchm@ext.jussieu.fr

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Abstract: Cyclic β-amino acids, homoproline, homopipecolic acid and 3-carboxy-methylmorpholine were obtained in high enantiomeric excesses by transition metal-catalyzed asymmetric hydrogenation of cyclic β-acylamino-alkenoates. These compounds were synthesized by a thio-Wittig reaction on N-protected thiolactames.

Key words: β-aminoacids, asymmetric synthesis, rhodium, ruthenium, iridium

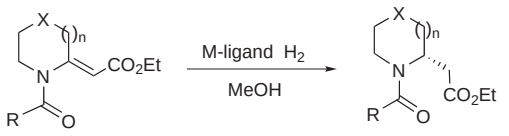
The synthesis of conformationally constrained amino acid derivatives has recently received much attention due to their ability to act as conformational probes when incorporated into peptides and peptidomimetics.[1] Among them, optically active β-amino acids, although of less importance than the parent α-amino acids, are crucial structural units of numerous biologically active and natural products.[2] Various methods are available for the synthesis of linear compounds of this series by both asymmetric synthesis and enzymatic resolutions.[3]

In contrast, there are few methods available for the asymmetric synthesis of cyclic β-amino acids. Some methods are known for the $\beta^{2,3}$-acids.[4] For the β^3-acids, Arndt–Eistert homologation of (*S*)-proline has been used to access to homoproline[5] and homopipecolic acid.[6] More recently, two general approaches to five- and six-membered cyclic β^3-amino acids have been disclosed using diastereo-controlled Michael additions of chiral amides to α,β-unsaturated esters followed by intramolecular ring-closure[7] and diastereoselective reduction of the resulting chiral β-enamino esters.[8]

Although linear β-amino acids may be obtained in high enantiomeric excesses by asymmetric hydrogenation of β-(acylamino)acrylates,[9] to the best of our knowledge, only the synthesis of homoproline by enantioselective hydrogenation has been reported until now.[10]

In this paper, we wish to describe a novel and efficient synthesis of N-protected homoproline, homopipecolic acid and 3-carboxymethylmorpholine by transition metal-catalyzed hydrogenation of cyclic enamido esters.

It is well known that the use of bidentate substrates is generally required to achieve highly enantioselective metal-catalyzed hydrogenations. Compounds **1**–**4** fit well with such requirement; they were then considered as substrates for enantioselective hydrogenations (Scheme 1).

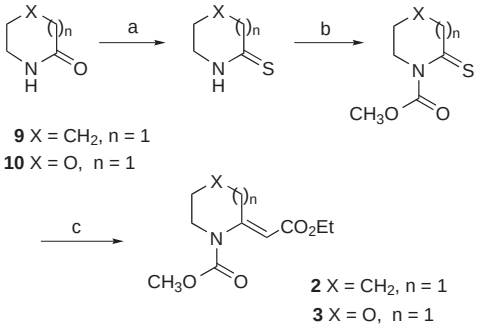


1 X = CH_2, n = 0, R = CH_3
2 X = CH_2, n = 1, R = OCH_3
3 X = O, n = 1, R = OCH_3
4 X = O, n = 1, R = O*t*-Bu
5 X = CH_2, n = 0, R = CH_3
6 X = CH_2, n = 1, R = OCH_3
7 X = O, n = 1, R = OCH_3
8 X = O, n = 1, R = O*t*-Bu

Scheme 1

In contrast with the linear β-acylamido acrylates the preparation of which is well known, the cyclic analogs are of a more difficult access. The synthesis of non-protected *Z*-enamino esters by addition of a Meldrum acid salt to a lactime ether was previously described by Lhommet et al.[11]

However, such a method is not general. Only the five-membered cyclic derivative **1** may be obtained by direct acylation of the nitrogen atom with acetyl chloride. The six- and seven-membered ring enamino esters are always acylated in position α to the ester function. Consequently, we have then developed an alternative method based on a thio-Wittig condensation[12] to access to the required compounds. The N-protected thiolactames prepared by thiolation of the corresponding lactones followed by protection of the nitrogen atom were reacted with a Wittig reagent to give mainly the *E*-isomers of the desired enamino esters **2** and **3** (Scheme 2).[13]



9 X = CH_2, n = 1
10 X = O, n = 1

2 X = CH_2, n = 1
3 X = O, n = 1

Scheme 2 (a) P_4S_{10}, Na_2CO_3, THF; (b) *n*-BuLi, THF, then $ClCO_2Me$, –78 °C to 0 °C; (c) $(C_6H_5)_3P$=CH-CO_2Et, refluxing toluene.

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With the exception of works reported by Noyori[9a] and more recently by Zhang,[9h] the reduction of enamido esters were generally achieved with rhodium-based catalysts. Therefore, in first experiments, the *N*-acetyl enamino ester **1** was hydrogenated in methanol with a Rh-MeDuphos complex (Table 1).

However, with this catalyst, we were unable to achieve total conversion. A somewhat better result was obtained with Et-FerroTANE,[14] which allowed an almost total conversion with an ee of 80%. We then turned our attention towards the use of ruthenium, which gave satisfactory results in the hydrogenation of various substrates.[15]

The method reported by Genêt was used to prepare the catalytic mixture, namely treatment [(COD)Ru(2-methylallyl)$_2$] with hydrobromic acid in the presence of the chiral ligand.[16] With MeO-Biphep, we succeeded in obtaining the ethyl homoprolinate **5** in high enantiomeric excess (entry 4). It must be outlined that increasing the H_2 pressure resulted in a slight decrease of the enantiomeric excess, a result in agreement with the literature data.[17]

In the case of the piperidino substrate **2**, the reaction was more complicated, and using ruthenium as metal, whatever the solvent used (MeOH, CH_2Cl_2, toluene), we observed the almost exclusive formation of a mixture of the β-keto ester **11** (Figure 1) resulting from the opening of the cycle and the corresponding reduced β-hydroxy ester. With rhodium-based catalysts generated in situ from $(COD)_2RhOTf$ and the chiral diphosphine, this side reaction was totally suppressed and the required ethyl homopipecolate was isolated in quantitative yield.

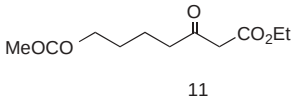

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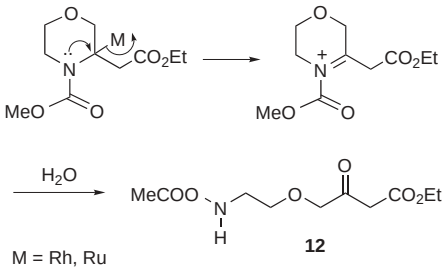
Figure 1

In contrast to the pyrrolidino substrate, the best enantioselectivity was obtained here with Et-FerroTANE (entry 10). Moreover, with atropoisomeric ligands the absolute configuration of the final product was opposite to that obtained during the reduction catalyzed with ruthenium: the (*S*)-enantiomer of MeO-Biphep led to the (*S*)-pipecolate.

In order to synthesize the previously unknown 3-carboxymethyl morpholine, we submitted the unsaturated ester **3** to enantioselective hydrogenation. However, in this case both rhodium and ruthenium afforded the ring-opening product, the β-keto ester **12**.



Scheme 3

Such a result may be explained by the intermediate formation of an acyl iminium salt resulting from an elimination reaction according to Scheme 3. We decided then to check the use of iridium complexes which are well known

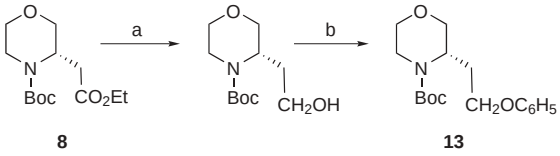
Table 1 Hydrogenation of Cyclic β-Enamidoesters **1** and **2**[a]

Entry	Substrate	M	Ligand	P (bar)	Conv. (%)	ee (%, conf.)[b]
1	**1**	Rh	(*R*,*R*)-MeDuPHOS	3	70	82 (*R*)
2	**1**	Rh	(*R*,*R*)-Et-FerroTANE	3	95	80 (*R*)
3	**1**	Ru	(*S*)-Binap	10	100	93.5 (*R*)
4	**1**	Ru	(*S*)-MeO-Biphep	10	100	97.3 (*R*)
5	**1**	Ru	(*S*)-MeO-Biphep	20	100	96.5 (*R*)
6	**2**	Rh	(*R*,*R*)-MeDuPHOS	3	30	95.5 (*R*)
7	**2**	Rh	(*R*,*S*)-Josiphos	15	100	14 (*R*)
8	**2**	Rh	(*R*)-Binap	16	100	85 (*R*)
9	**2**	Rh	(*R*,*R*)-MeDuPHOS	12	100	93.2 (*R*)
10	**2**	Rh	(*R*,*R*)-Et-FerroTANE	15	100	95.1 (*R*)
11	**2**	Rh	(*S*)-MeO-Biphep	16	100	91.4 (*S*)

[a] Reactions were carried out by stirring a mixture of substrate (1 mmol) and catalyst (1%) under H_2 in MeOH for entries 1–5 and CH_2Cl_2 for entries 6–11.
[b] The ee values were determined by GC on a chiral Chirasil-DEX CB column (Varian).

catalysts for the reduction of some C-C double bonds[18] and imines.[19] This metal indeed avoided the formation of the keto ester. However, using Binap or MeO-Biphep, the required carbethoxymethyl morpholine was obtained in a maximum ee of only 75% (Table 2, entry 3). Such a result was perhaps due to the fact that the unsaturated ester was not stereochemically pure (*E*:*Z* ratio = 87:13).

In the case of the *N*-Boc protected substrate **4**, which was prepared as the pure *E*-isomer,[20] we were pleased to isolate the saturated ester in somewhat higher enantiomeric excesses. The best result was measured as a 85.5% ee with Tol-Binap.[21] Surprisingly, the use of the Pfaltz's ligand Phox gave exclusively the ring-opening adduct **12**.



Scheme 4 (a) DIBALH 1 M in toluene (2 equiv), Et_2O, 0 °C, 1 h; (b) phenol (1.5 equiv), $(C_6H_5)_3P$ (1.5 equiv), DIAD (1.5 equiv), THF, 0 °C, 2.5 h, 63%.

The absolute configuration of compound **8** was determined by chemical correlation. The ester was reduced into the corresponding alcohol and transformed into the ether **13** using a Mitsunobu substitution reaction (Scheme 4). Comparison of the rotatory power of this ether with the value previously reported for the same compound prepared from serine[22] allowed us to assign the *S* configuration to the hydrogenation product **8**.

The enantiomeric excess was upgraded to 99% by saponification of the ester **8** and recrystallization of the corresponding *N*-Boc protected β-amino acid.[23]

Concerning the stereochemical outcomes of the hydrogenations catalyzed by ruthenium complexes, they are in agreement with the quadrant diagram proposed by Noyori.[24] If we transpose to β-enamino esters the model used for α-enamino esters,[25] the steric interaction between the substituent in α position to the amido group (the ring carbons in complex **A** and **B**) and the equatorial phenyl groups of the ligand should determine the relative stability of the enamido complexes (Figure 2).

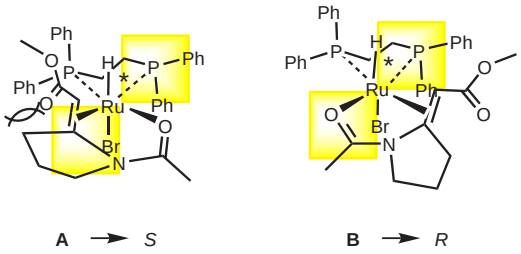


Figure 2 Reaction intermediates for metal complexes with δ-conformation [(*S*)-BINAP].

The more stable intermediate **B** is expected to afford an *R* configurated β-amino ester as the major final product. This is in agreement with the experimental results reported above. If the same stability criteria are applied to the [(*R*,*R*)-MeDuPHOS]Rh-(**2**) complexes, it appears that in this case the hydrogenation reaction is under kinetic control and that the less stable complex is hydrogenated more quickly than the more stable one to afford the major *R*-enantiomer. These results are in agreement with the mechanism generally postulated for the hydrogenation of dehydro α-amino esters with rhodium catalyst[26] as well as with the stereochemical outcome of the reported hydrogenations of acyclic β-enamino esters.[9e]

In summary, homoproline, homopipecolic acid and 3-carboxymethylmorpholine were obtained in high enantiomeric excesses by metal-catalyzed asymmetric hydrogenation of cyclic β-acylamino alkenoates, which were synthesized by a thio-Wittig reaction on N-protected thiolactames. For each single substrate, high enantioselectivities are attained by a very specific appropriate choice of the metal–ligand pairs used in the hydrogenation step.

Acknowledgment

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Table 2 Hydrogenation of Cyclic β-Enamidoester **3** and **4** with Iridium Complexes[a]

Entry	Substrate	Ligand	P (bar)	Conv. (%)	Product	ee (%, conf.)
1	**3**	(*R*,*R*)-Et-FerroTANE	50	80	**7**	7 (*R*)
2	**3**	(*S*)-MeO-Biphep	50	35	**7**	66 (*S*)
3	**3**	(*S*)-Binap	50	85[b]	**7**	75 (*S*)
4	**4**	(*R*,*S*)-Josiphos	40	80	**8**	4
5	**4**	(*S*)-Binap	50	100	**8**	79 (*S*)
6	**4**	(*S*)-Tol-Binap	50	100	**8**	85.5 (*S*)

[a] Reactions were carried out by stirring a mixture of substrate (1 mmol) and catalyst (1%) under H_2 in MeOH for entries 1–3 and CH_2Cl_2 for entries 4, 5 (in CH_2Cl_2–THF 1:4 for entry 6).
[b] It contains 60% of 3-carbethoxymethyl-5,6,-dihydro-4-methoxycarbonyl-[1,4]oxazine.

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(13) Yields from the corresponding N-protected thiolactames: compound **2**: 60% (*E*: 100%); compound **3**: 55% (*E*:*Z* = 87:13). The reaction failed with hindered protective groups such as Boc.

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(20) Compound **4** was obtained as the pure *E*-isomer using the reaction of a Peterson reagent ($Me_3SiCHLi$-CO_2Et) with the N-protected δ-lactone.

(21) **Typical Procedures: Ruthenium**: [(COD)Ru(2-methylallyl)$_2$] (0.01 mmol, 3.2 mg, 1 equiv) and (*S*,*S*)-MeO-Biphep (0.012 mmol, 7 mg, 1.2 equiv) were stirred under argon for 30 min in acetone (1 mL), 0.16 N HBr in MeOH (140 μL, 2.2 equiv) was then slowly added and the solution was stirred for 30 min at r.t. The unsaturated enamido ester (100 equiv) was then added and the solution was transferred into an autoclave. The autoclave was then purged three times with hydrogen and filled with hydrogen at the required pressure. The mixture was stirred at r.t. for 24 h. After release of the hydrogen, the solvent was evaporated. The residue was passed through a short silica gel plug to give the reducted β-amino esters.
Rhodium: [(*R*,*R*)-(Me-DuPHOS)Rh(COD)(OTf)] (0.01 mmol, 6.6 mg, 1 equiv) was stirred under argon in degassed CH_2Cl_2 (1 mL) at r.t. The unsaturated enamido ester (100 equiv) in CH_2Cl_2 was then added and the solution was transferred into an autoclave and treated as previously described.
Iridium: [(COD)Ir(Cl)]$_2$ (0.05 mmol, 3.4 mg, 0.5 equiv) and (*S*)-BINAP (0.012 mmol, 7.5 mg, 1.2 equiv) were stirred under argon in a glass tube for 30 min in degassed CH_2Cl_2 (2 mL), the unsaturated enamido ester (100 equiv) was then added, the glass tube was transferred into an autoclave and treated as previously described.
Physical Data: compound **5**: $[\alpha]_D^{20}$ +58.5 (*c* 2.3, CH_2Cl_2), ee: 97.3%. IR (KBr): 2955, 1737, 1698, 1452, 1385, 1194 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$), two conformers: δ = 1.23, 1.25 (2 t, 3 H, *J* = 7.1 and 7.2 Hz), 1.73–2.11 (m, 4 H), 2.01, 2.10 (2 s, 3 H), 2.31, 2.41, 2.54, 2.94 (4 dd, 2 × 2 H, *J* = 3.9, 9.5, 15.4 and 3.6, 10.3, 15.4 Hz), 3.43 (m, 2 H), 4.12 (2 q, 2 H, *J* = 7.1 and 7.2 Hz), 4.23, 4.38 (2 m, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 23.0, 23.9, 30.1, 37.6, 47.9, 53.8, 60.4, 169.3, 171.5. MS (CI, NH_3): *m/z* (%) = 217

(100) [M + 1], 200(23). Compound **6**: $[\alpha]_D^{20}$ +13.7 (*c* 4.0, $CHCl_3$), ee: 95.1%. IR (KBr): 2976, 1735, 1701, 1413, 1392, 1163 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.23 (t, 3 H, *J* = 7.1 Hz), 1.40–1.60 (m, 6 H), 2.51 (dd, 2 H, *J* = 8.0 and 14.3 Hz), 2.81 (dd, 1 H, *J* = 7.4 and 14.3 Hz), 2.83 (t, 1 H, *J* = 11.5 Hz), 3.66 (s, 3 H), 4.07 (br s, 1 H), 4.09 (q, 2 H, *J* = 7.2 Hz), 4.72 (br s, 1 H). ^{13}C NMR (50 MHz, D_2O): δ = 21.5, 21.9, 28.2, 40.0, 44.6, 54.6, 177.7. MS (CI): *m*/*z* = 144. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.48; H, 8.53; N, 6.02.

(2*R*)-2-Carboxymethylpiperidine: The ester **6** (0.5 mmol) was saponified at r.t. with KOH (2.75 mmol, 5.5 equiv) in solution in a EtOH (3.5 mL)–H_2O (0.75 mL) mixture for 48 h. After evaporation, the solid residue was then treated with HBr in HOAc (33%) for 24 h. After elimination of the HOAc under vacuo, the residue was chromatographed on Dowex H^+ 50X8 resin (2 M aq NH_3) to give a white solid (70%): mp 95 °C (hexane); $[\alpha]_D^{20}$ –28 (*c* 0.60, H_2O), lit.[6] 93 °C; *S* compound $[\alpha]_D^{20}$ +33.5 (*c* 0.60, H_2O). IR (KBr): 3500–3200, 3011, 2980, 1736, 1639, 1433, 1185 cm^{-1}. ^1H NMR (200 MHz, D_2O): δ = 1.41 (m, 3 H), 1.76 (m, 3 H), 2.37 (d, 2 H, *J* = 6.7 and 15.0 Hz), 2.89 (td, 1 H, *J* = 12.6 and 12.7), 3.28 (m, 2 H). ^{13}C NMR (50 MHz, D_2O): δ = 21.5, 21.9, 28.2, 40.0, 44.6, 54.6, 177.7. MS (CI): *m*/*z* = 144. Compound **8**: $[\alpha]_D^{20}$ +30.2 (*c* 1.15, CH_2Cl_2), ee: 85.5%. IR (KBr): 2980, 1735, 1698 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.1 Hz, 3 H), 1.44 (s, 9 H), 2.54 (dd, *J* = 5.5 and 15.0 Hz, 1 H), 2.81 (dd, *J* = 8.8 and 15.0 Hz, 3 H), 4.11 (q, *J* = 7.1 Hz, 2 H), 4.36 (m, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 28.4, 33.8, 39.5, 48.1, 60.7, 66.9, 68.9, 80.3, 154.5, 171.3. MS (EI): *m*/*z* (%) = 273 (1), 217 (5), 200 (3), 172 (24), 142 (43), 130 (32), 86 (46), 57 (100), 41 (26). Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 57.06; H, 8.63; N, 5.04.

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(23) **(3*S*)-4-*tert*-Butoxycarbonyl-3-carboxymethylmorpholine:** mp 82 °C (hexane–*i*-Pr_2O, 8:2); $[\alpha]_D^{20}$ +35.7 (*c* 1.94, CH_2Cl_2), ee: 99%. IR (KBr): 3700–2500, 1713, 1694 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.47 (s, 9 H), 2.56 (dd, *J* = 6.0 and 15.4 Hz, 1 H), 2.83 (dd, *J* = 8.5 and 15.4 Hz, 1 H), 2.90–3.90 (m, 6 H), 4.34 (m, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.2, 33.4, 39.4, 48.0, 66.7, 68.8, 80.5, 154.5, 175.9. MS (EI): *m*/*z* (%) = 245 (1), 190 (2), 172 (3), 130 (14), 114 (13), 100 (5), 86 (33), 70 (13), 57 (100). Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.71. Found: C, 53.95; H, 7.91; N, 5.59.

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