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Enantioselective Henry Addition of Methyl 4-Nitrobutyrate to Aldehydes. Chiral Building Blocks for 2-Pyrrolidinones and Other Derivatives

Gonzalo Blay,* Víctor Hernández-Olmos, and José R. Pedro*

Departament de Química Orgànica, Facultat de Química, Universitat de València, C/Dr. Moliner, 50, E-46100 Burjassot (València), Spain
gonzalo.blay@uv.es; jose.r.pedro@uv.es

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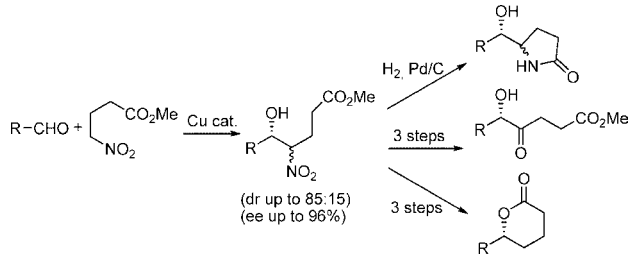
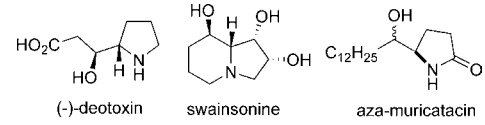
ABSTRACT



A catalytic highly enantioselective Henry addition of methyl 4-nitrobutyrate to aldehydes using a Cu(II)−amino pyridine complex as catalyst is described. The products resulting from this reaction constitute a new, highly versatile family of chiral building blocks as a result of the presence of three different functional groups on the molecule. These products have been transformed into nonracemic chiral γ-lactams, 5-hydroxy-5-substituted levulinic acid derivatives, and δ-lactones.

Organic molecules containing chiral pyrrolidine and 2-pyrrolidinone (γ-lactam) heterocycles are common among natural products and pharmaceuticals with structures ranging from the simple to the architecturally complex.[1] These heterocyclic compounds are also important building blocks for the synthesis of complex natural products[2] and other heterocycles,[3] and the biological activity of these compounds is strongly modulated by the ring substitution pattern and its absolute stereochemistry. In particular, the 5-(1′-hydroxyalkyl)pyrrolidinone and the 2-(1′-hydroxyalkyl)pyrrolidine (prolinol) moieties can be found in several natural products such as the unusual amino acid (−)-detoxinine,[4] indolizinic alkaloids such as swainsonine,[5] or the antitumoral agent aza-muricatacin (Figure 1).[6]

Compounds bearing this moiety have also been used as organocatalysts[7] and chiral ligands in metal-catalyzed enantioselective reactions.[8] Therefore, the development of procedures to obtain them, especially in enantiomerically pure form, constitutes an appealing goal. These compounds have been mainly synthesized by functional modification of the parent five-membered heterocycles. Examples include modifications of proline and pyroglutamic acid,[3,7] hydroxyalkylation of 2-silyloxypyrroles and pyrrolidinones with aldehydes,[2c,d,i,9] and the hydroxylation of 5-alkylidene-2-pyrrolidinones.[10] Furthermore, some examples in which the heterocyclic ring is formed via cyclization reactions have



(-)-deotoxin swainsonine aza-muricatacin

Figure 1. Natural and bioactive hydroxyalkyl pirrolidines and pyrrolidinones.

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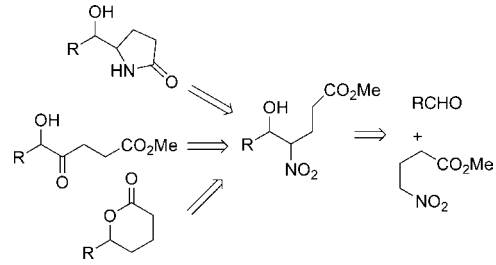
been described.[4c,11] Despite this, only a few of these procedures provide the expected hydroxyalkyl-γ-lactams and prolinols in a highly enantioselective way.

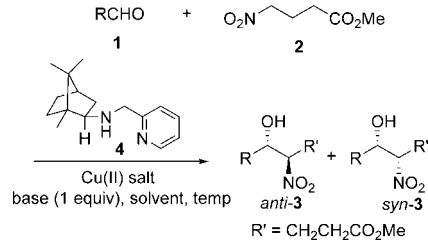
The construction of multifunctional chiral building blocks that can provide access to different structural motifs has raised much interest among synthetic chemists. The Henry (nitro-aldol) reaction is a straightforward way to prepare β-hydroxy nitroalkanes that are versatile building blocks as a result of the chemical versatility of both the hydroxyl and the nitro groups. In recent years there has been much progress in the development of enantioselective versions of the Henry reaction, especially using nitromethane and other unfunctionalized nitroalkanes.[12] However, the number of enantioselective procedures described with functionalized nitroalkanes is rather scarce. In this Letter we describe the enantioselective Henry reaction between aldehydes and methyl 4-nitrobutyrate and the transformation of the resulting products into chiral nonracemic γ-lactams, levulinic acid derivatives, and δ-lactones (Scheme 1).

Scheme 1. Synthetic Applications of the Henry Products between Aldehydes and Methyl 4-Nitrobutyrate



Recently our group has developed camphor-derived C_1-symmetric amino pyridine ligands **4** that in the presence of Cu(II) salts catalyze the addition of nitroalkanes to aldehydes with very high enantioselectivity (up to 98% ee) under very advantageous experimental conditions.[13] When these conditions were applied to the reaction of benzaldehyde (**1a**) and methyl 4-nitrobutyrate (**2**), compound **3a** was obtained as an *anti*:*syn* 67:33 diastereomeric mixture with 92% and 91% ee, respectively (Scheme 2, Table 1, entry 1). Further optimization was

Scheme 2. Henry Reaction between Aldehydes and Methyl 4-Nitrobutyrate Catalyzed by **4**−Cu(II) Complexes



carried out by changing solvent, copper salt, and base (Table 1). The best result was reached with $Cu(OTf)_2$ and Et_3N in MeOH (entry 8), which produced compound **3a** as an *anti:*syn 85:15 diastereomeric mixture with 96% and 90% ee, respectively. We also checked the reaction with *tert*-butyl 4-nitrobutyrate and obtained the corresponding product in excellent yield but lower stereoselectively than with methyl ester **2** (entry 9).

The scope of the reaction under the optimized conditions was studied with a number of aldehydes (Table 2). The reaction temperature was adjusted according to the reactivity of the

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Table 1. Henry Reaction between Benzaldehyde (**1a**, R = Ph) and Methyl 4-Nitrobutyrate (**2**) Catalyzed by **4**-Cu(II)[a]

entry	Cu(II) salt	base	solvent	temp (°C)	time (h)	*anti:syn*[b]	ee (% *anti/syn*)[c]
1	$Cu(OAc)_2$	DIPEA	EtOH	−45	48	67:33	92/91
2	$Cu(OAc)_2$	DIPEA	MeOH	−45	17	83:17	95/80
3	$Cu(OAc)_2$	DIPEA	THF	−25	24	56:44	94/95
4	$Cu(OAc)_2$	DIPEA	toluene	−35	24	56:44	92/95
5	$Cu(OAc)_2$	DIPEA	CH_2Cl_2	−35	40	41:59	79/93
6	$Cu(OTf)_2$	DIPEA	MeOH	−45	16	85:15	95/87
7	$Cu(OTf)_2$	Bu_3N	MeOH	−45	19	85:15	96/86
8	$Cu(OTf)_2$	Et_3N	MeOH	−45	17	85:15	96/90
9[d]	$Cu(OTf)_2$	Et_3N	MeOH	−45	22	76:24	88/84

[a] **4** (11 mol %), Cu(II) salt (10 mol %), **2** (10 equiv), base (1 equiv). [b] Determined by ^{1}H NMR. Full conversion. [c] Determined by chiral HPLC. [d] Reaction carried out with *tert*-butyl 4-nitrobutyrate.

Table 2. Henry Reaction between Aldehydes **1** and Methyl 4-Nitrobutyrate (**2**) Catalyzed by **4**-$Cu(OTf)_2$[a]

entry	**2**	R	temp (°C)	time (h)	**3**	yield (%)[b]	*anti:syn*[c]	ee (%)[d] *anti*/*syn*
1	**a**	Ph	−45	17	**a**	99	85:15	96/90
2	**b**	2-$MeOC_6H_4$	−45	17	**b**	99	77:23	96/93
3	**c**	2-ClC_6H_4	−45	21	**c**	99	85:15	93/74
4	**d**	4-$MeOC_6H_4$	−45	43	**d**	95	76:24	90/82
5	**e**	4-ClC_6H_4	−45	25	**e**	99	84:16	95/76
6	**f**	4-$NO_2C_6H_4$	−45	20	**f**	99	81:19	88/56
7	**g**	4-MeC_6H_4	−45	20	**g**	98	81:19	95/86
8	**h**	3-$MeOC_6H_4$	−45	21	**h**	99	80:20	95/85
9	**i**	3-ClC_6H_4	−45	19	**i**	99	85:15	95/76
10	**j**	Ph-CH=CH	−45	18	**j**	99	74:26	91/62
11	**k**	cyclohexyl	−5	22	**k**	67	26:74	54/87
12	**l**	$PhCH_2CH_2$	−5	70	**l**	86	43:57	49/59

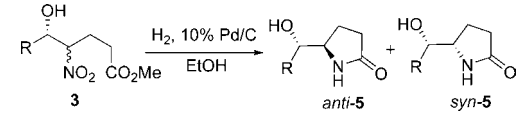
[a] **4** (11 mol %), $Cu(OTf)_2$ (10 mol %), **2** (10 equiv), Et_3N (1 equiv), MeOH. [b] Yield of isolated product. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC. Absolute stereochemistry assigned according to reference.[13]

aldehyde. With aromatic aldehydes, the reaction provided the expected products **3** in high to quantitative yields, fair to good diastereoselectivities and excellent enantioselectivities, with ee values above 90% for the major diastereoisomer in most cases, regardless of the electronic nature and location of the substituent on the aromatic ring (entries 1−5 and 7−9). Only the presence of a strongly electron-withdrawing nitro group (entry 6) brought about a small decrease in the enantioselectivity especially in the minor diastereoisomer. Most remarkably, the reaction could also be performed with unbranched and even branched aliphatic aldehydes (entries 11 and 12). In these cases, the reaction had to be carried out at higher temperature (−5 °C), and the resulting products were obtained in high yields but lower stereoselectivity than with aromatic aldehydes. The reaction with the unsaturated aldehyde **1j** exclusively afforded the 1,2-addition product with good stereoselectivity (entry 10).

With nitroalkanols **3** in hand, we studied their transformation into γ-lactams. Reduction of the nitro group was carried out by hydrogenation on 10% Pd/C to give directly the desired γ-lactams **5** (Scheme 3).

We carried out the lactamization reaction with a representative number of compounds **3**, obtaining the expected lactams **5** with yields around 70% (Table 3). We observed small changes in the diastereomeric ratios of products **5** with respect to the diastereomeric ratios of the starting materials **3**. Normally a little increase in the percentage of the *anti* isomer was observed in most cases, except for compound **5f**. A possible explanation for this change could be a slight epimerization or the retro-Henry reaction of one of the diastereomers during storage.[14]

Scheme 3. Synthesis of γ-Lactams by Hydrogenation of Compounds **3**



The Henry reaction−lactamization sequence has been applied to a short synthesis of *syn*- and *anti*-aza-muricatacin (**5m**), which are compounds with an important antitumoral activity (Scheme 4).[6] The synthesis was carried out from tridecanal (**1m**). Because of the low solubility of **1m** in MeOH, the **4**-copper(II)-catalyzed Henry reaction was carried out in EtOH at −10 °C, giving compound **3m** in 90% yield as a 36:64 *anti*:*syn* mixture

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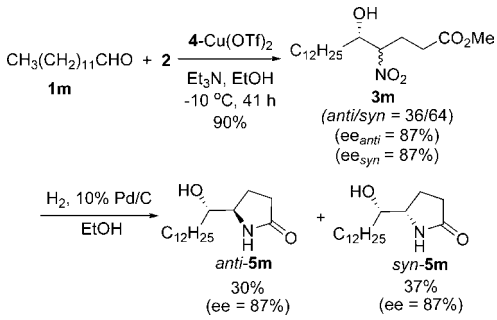
Table 3. Representative Examples of Lactamization of Compounds **3** According to Scheme 3

entry	**3**	R	time (h)	**5**	yield (%)[a]	*anti:syn*[b]	ee (%)[c] *anti*/*syn*
1	**A**	Ph	23	**a**	70	89:11	96/80
2	**B**	2-$MeOC_6H_4$	25	**b**	75	80:20	96/94
3	**D**	4-$MeOC_6H_4$	25	**d**	66	80:20	90/84
4[d]	**F**	4-$NO_2C_6H_4$	25	**f**	66	63:37	85/55
5	**G**	4-MeC_6H_4	41	**g**	73	85:15	94/75
6	**H**	3-$MeOC_6H_4$	26	**i**	74	84:16	94/85
7	**K**	cyclohexyl	41	**k**	65	26:74	56/85

[a] Yield of isolated product. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC. [d] Reduction of the aromatic nitro group also took place.

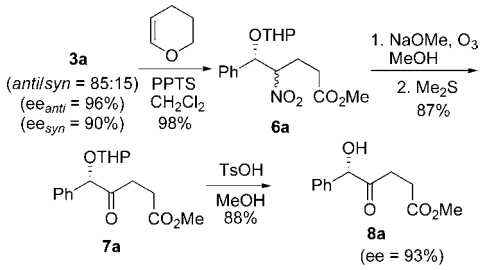
with 87% ee for both diastereomers. Hydrogenation of the mixture gave *syn*-**5m** and *anti*-**5m**, which were separated by HPLC. It should be mentioned that this is the shortest synthesis of aza-muricatacin reported so far.

Scheme 4. Enantioselective Synthesis of Aza-muricatacin



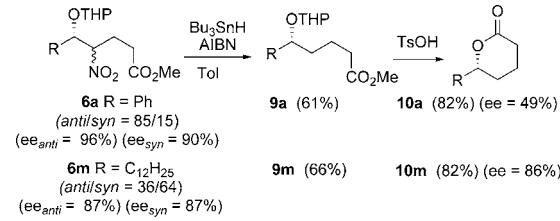
To explore the synthetic versatility of compounds **3** as chiral building blocks, we have also carried out the synthesis of 5-hydroxy-5-phenyllevulinic acid methyl ester (**8a**), a compound with known analgesic activity (Scheme 5).[15] In this case the hydroxyl group needed to be protected as a THP ether in order to avoid a retro-Henry reaction. Ozonolysis of the nitronate gave ketone **7a** in 87% yield. Finally deprotection of the hydroxyl group afforded compound **8a** with 93% ee.

Scheme 5. Enantioselective Synthesis of 5-Hydroxy-5-phenyllevulinic Acid Methyl Ester



δ-Lactones are also available from compounds **3** (Scheme 6). Denitration of compound **6a** was achieved upon treatment with Bu_3SnH/AIBN to give **7a** in 61% yield, which after deprotection of the hydroxyl group under acidic conditions gave lactone **10a**.[16] Unfortunately, the compound was obtained with only 49% ee, indicating a partial racemization of the C-OH atom, probably due to formation of stabilized benzyl radicals. As a matter of fact, using a similar sequence, starting from compound **6m**, derived from an aliphatic aldehyde, lactone **10m** was obtained, this time without any loss of enantiomeric purity with respect to the starting material.

Scheme 6. Enantioselective Synthesis of *δ*-Lactones



In summary, we have prepared a new highly versatile family of chiral building blocks via a catalytic enantioselective Henry reaction of aldehydes with methyl 4-nitrobutyrate. The synthetic applicability of these new building blocks has been shown with the synthesis of chiral *γ*-lactams, 5-hydroxy-5-phenyllevulinic acid methyl ester, and *δ*-lactones with high ee (up to 96% ee).

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Supporting Information Available: Representative experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra and chiral analysis for compounds **3**, **5**, **8**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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