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Stereoselective synthesis of 2-amino-5-hydroxycaprolactams from L-glutamic acid

Didier Roche, Kapa Prasad,* Oljan Repic and Thomas J. Blacklock

Process Research & Development, Chemical & Analytical Development, Novartis Institute for Biomedical Research, East Hanover, NJ 07936, USA

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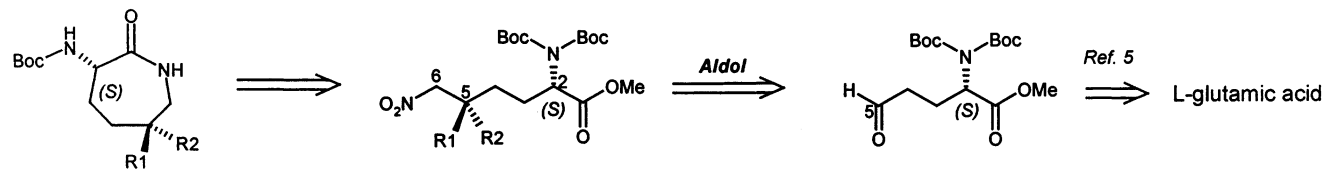
Abstract—A five-step stereoselective synthesis of both (2*S*,5*S*)- and (2*S*,5*R*)-2-amino-5-hydroxycaprolactam has been achieved via the aldol reaction of L-glutamic aldehyde **1** with nitromethane. © 2001 Elsevier Science Ltd. All rights reserved.

5-Hydroxylysine is an amino acid which is found in collagen, and its cyclic form, 2-amino-5-hydroxycaprolactam, is an important constituent of a recently identified anti-tumor agent belonging to the bengamide marine sponge natural products.[1a–c] Whereas the (2*S*,5*S*)-2-amino-5-hydroxycaprolactam is found in natural bengamides,[1a–c] the (2*S*,5*R*)-diastereomer has been used for the synthesis of analogs.[2] It was therefore of interest to design a synthesis that offered the flexibility of having either the (*S*) or (*R*) configuration at the C5 atom. The syntheses that have been reported in the literature lack this flexibility and are too long (14–20 steps).[3a–c,4] We wish to report herein a five-step stereoselective synthesis of both (2*S*,5*S*)- and (2*S*,5*R*)-2-amino-5-hydroxycaprolactam from the readily available glutamic aldehyde **1**. Our approach relies on a selective nitro-aldol reaction of **1** with nitromethane.

Glutamic aldehyde **1** was obtained in three steps and 76% overall yield from L-glutamic acid according to Ref. 5. Nitro-aldol reaction of **1** with nitromethane was then investigated to introduce the C5 stereogenic center. The results are presented in Table 1. As one could expect, nitro-aldol reaction of **1** with nitromethane in Et_3N gave no selectivity (entry 1). Therefore, our effort focused on the catalytic asymmetric methodology developed by Shibasaki using an enantiopure bis-metallic binaphthol (BINOL) complex as the catalyst.[6a–m] The catalyst was prepared using different methods derived from Shibasaki's work and from different sources of lanthanum ($LaCl_3 \cdot 7H_2O$, La(O*i*Pr)$_3$ or La(2-ethylhexenoate)$_3$). The nitro-aldol reaction appeared to be clean and provided good yields of nitro-aldol adduct in the presence of an excess of nitromethane (reaction with 1.1 equiv. failed, entry 7) and 5–10% of catalyst in THF. The selectivity, however, appeared to be strongly dependent upon the method used in making the lanthanum–lithium–BINOL catalyst (LLB). When $LaCl_3 \cdot 7H_2O$ was used as a source of lanthanum, the best ratio of diastereomers (81/19 *SR*/*SS*)[7] was obtained using the catalyst prepared by method C[6d] and based on a 1/1 mixture of $LaCl_3 \cdot 7H_2O$ and dilithium salt of (*S*)-(−)-BINOL (entry 4).

Higher selectivity was obtained when the catalyst was prepared from a 1/3 mixture of La(O*i*Pr)$_3$ and the mono-lithium salt of (*S*)-(−)-BINOL (method D).[6c] The 87/13 mixture of (*SR*/*SS*)-diastereomers obtained with 5% of catalyst (entry 5) was further improved to 91/9 using 10% of catalyst (entry 6). When the enantiomer of catalyst LLB was prepared according to the same method D, a small mismatch effect was observed in the nitro-aldol reaction, which provided the desired



R1 = OH, R2 = H (2*S*,5*S*)-**3**
R1 = H, R2 = OH (2*S*,5*R*)-**3**

R1 = H, R2 = OH (2*S*,5*S*)-**2**
R1 = OH, R2 = H (2*S*,5*R*)-**2**

1

* Corresponding author.

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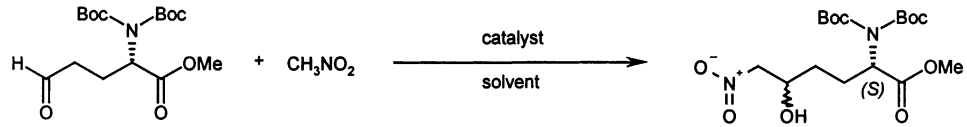
Table 1. Asymmetric nitro-aldol reaction of **1** with nitromethane

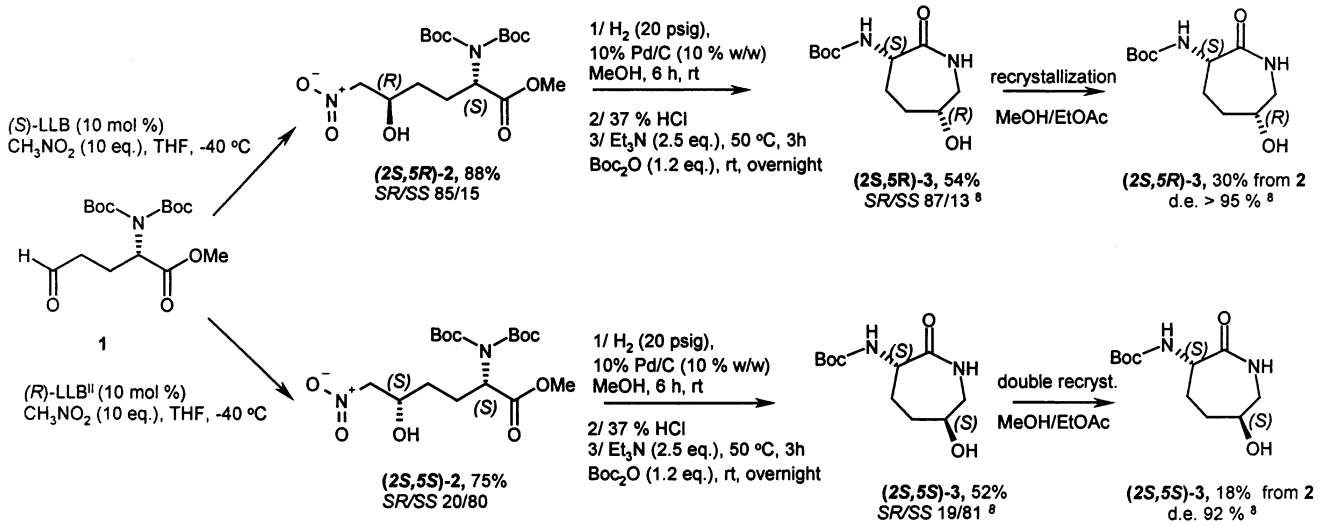


1 **2**

Entry	Catalyst	Method	La	Loading (%)	CH_3NO_2 (equiv.)	Solvent	Temp. (°C)	t (h)	SR/SS[c,d]	**6**, Yield (%)
1	Et_3N				10	Et_3N	Rt	50	48/52	74
2	(*R*)-LLB	A	$LaCl_3{\cdot}7H_2O$	10	10	THF	−40	96	Nd	<5[b]
3	(*S*)-LLB	B	$LaCl_3{\cdot}7H_2O$	10	10	THF	−40	16.5	54/46	52[a]
4	(*S*)-LLB	C	$LaCl_3{\cdot}7H_2O$	5	10	THF	−50	47	81/19	80[b]
5	(*S*)-LLB	D	La(O*i*Pr)$_3$	5	10	THF	−50	23	87/13	85[a]
6	(*S*)-LLB	D	La(O*i*Pr)$_3$	10	10	THF	−40	17	91/9	80[b]
7	(*S*)-LLB	D	La(O*i*Pr)$_3$	5	1.1	THF	−40	72	Nd	5[b]
8	(*R*)-LLB	D	La(O*i*Pr)$_3$	5	10	THF	−40	72	17/83	80[b]
9	(*R*)-LLB[II]	G	La(O*i*Pr)$_3$	10	10	THF	−50	48	20/80	75[a]
10	(*S*)-LLB	E	La(2-ethylhexenoate)$_3$	5	10	THF	−40	120	60/40	80[b]
11	(*R*)-LLB	F	La(O*i*Pr)$_3$	10	10	THF	−50	7	47/53	80[b]
12	(*R*)-LLB	H	La(O*i*Pr)$_3$	10	10	THF	−50	48	Nd	5[b]

Method A: $LaCl_3{\cdot}7H_2O$/BINOL/*n*BuLi/*t*BuONa 1/2.7/5.4/0.3, THF, 50°C, 48 h.[6m]
Method B: $LaCl_3{\cdot}7H_2O$/BINOL/NaOH 1/3/3, THF, rt, overnight.
Method C: $LaCl_3{\cdot}7H_2O$/BINOL/*n*BuLi/H_2O/*t*BuONa 1/1/2/4/1, THF, rt, overnight.[6d]
Method D: La(O*i*Pr)$_3$/BINOL/*n*BuLi/H_2O 1/3/1/1, THF, rt, overnight.[6c]
Method E: La(2-ethylhexenoate)$_3$/BINOL/*n*BuLi 1/3/6, THF, rt, overnight.
Method F: La(O*i*Pr)$_3$/BINOL/*t*BuOK 1/2.85/4.2, THF, rt, 2 h.
Method G: La(O*i*Pr)$_3$/BINOL/*n*BuLi 1/2.85/2.85 THF, rt, overnight then H_2O/*n*BuLi 1/0.6, rt, 1 h.[6k]
Method H: La(O*i*Pr)$_3$/BINOL/*t*BuMgCl 1/2.85/3.5, THF, rt, overnight.

[a] Isolated yield.
[b] Estimation based on ^1H NMR.
[c] Determined by ^{13}C NMR.
[d] Assignment of the C5 absolute configuration was made according to Ref. 7.



Scheme 1. Synthesis of (2*S*,5*S*)- and (2*S*,5*R*)-**3** from L-glutamic aldehyde **1**.

(2*S*,5*S*)-diastereomer (17/83 *SR*/*SS* ratio, entry 8). The use of 'second generation' (*R*)-LLB^{II}, prepared according to method G,[6k] did not improve the selectivity (entry 9). Further attempts to use La(2-ethylhexenoate)$_3$ as a source of lanthanum, potassium ((*R*)-LPB, method F) or magnesium ((*R*)-LMB, method H) as co-metals gave low selectivities (entries 10 and 11) or no reaction (entry 12).

Our optimized conditions (entry 6, Table 1) were then applied to the synthesis of the (2*S*,5*S*)- and (2*S*,5*R*)-2-amino-5-hydroxycaprolactam **3** (Scheme 1). Nitro-aldol reaction of **1** with nitromethane in the presence of 10% of (*S*)-LLB gave the desired nitro-aldol adduct (2*S*,5*R*)-**2** with 88% yield and 70% d.e. (note the change in selectivity from 82% d.e. in entry 6, Table 1, which was attributed to either the scale up of the reaction or some unknown factor and was not examined further). Reduction of the nitro group using 10% Pd/C, H_2 provided the (2*S*,5*R*)-5-hydroxylysine, which was directly deprotected, cyclized and reprotected to give (2*S*,5*R*)-**3** in 54% yield and 74% d.e.[8] The pure (2*S*,5*R*)-**3** diastereomer could be obtained after recrystallization from a mixture of EtOAc and MeOH (30% from **2**). Similarly, the (*R*)-LLB^{II} catalyst prepared by method G provided the (2*S*,5*S*)-**2** nitro-aldol adduct in 75% yield and 60% d.e. in good agreement with the optimized conditions. The consecutive sequence of reactions, as mentioned above, led to the (2*S*,5*S*)-**3** diastereomer with 54% yield and 62% d.e. Double recrystallization from MeOH/EtOAc led to (2*S*,5*S*)-**3a** (92% d.e.) in 18% yield from the nitro-aldol intermediate (2*S*,5*R*)-**2**.

In conclusion, we have designed a short stereoselective synthesis of the caprolactam unit of both natural and unnatural bengamides. The synthesis utilizes Shibasaki's catalytic asymmetric nitro-aldol reaction with nitromethane and the easily accessible glutamic aldehyde **1**. The (*R*)-LLB catalyst gives the (*S*)-C5 stereochemistry with 60% d.e., whereas the (*S*)-LLB catalyst gives the (2*S*,5*R*)-diastereomer with 70% d.e. After cyclization and recrystallization (2*S*,5*R*)- and (2*S*,5*S*)-2-amino-5-hydroxycaprolactam **3** were obtained with a d.e. of >95 and 92%, respectively.

Acknowledgements

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7. The absolute configuration at C5 was determined by comparison with authentic samples made from commercially available (2*S*,5*R*)-hydroxylysine (F. R. Kinder et al., ACS abstract No. 263, 220th ACS National meeting, Washington, DC, August 20–24, 2000). ^{1}H NMR data (300 MHz, DMSO-d_6): **(2*S*,5*R*)-3**: 7.42 (t, $J=6$ Hz, 1H), 6.39 (d, $J=5.5$ Hz, 1H), 4.61 (d, $J=3.6$, Hz, 1H), 4.06 (m, 1H), 3.73 (m, 1H), 3.37 (m, 1H), 3.01 (m, 1H), and 1.45–1.88 (m, 4H), 1.40 (s, 9H); **(2*S*,5*S*)-3**: 7.75 (t, $J=6$ Hz, 1H), 6.40 (d, $J=6$ Hz, 1H), 4.92 (d, $J=3.6$, Hz, 1H), 4.13 (m, 1H), 3.30 (m, 1H), 3.16 (m, 1H), 2.95 (m, 1H), 2.03 (m, 1H), 1.80 (m, 1H), 1.5–1.7 (m, 2H), and 1.45 (s, 9H).
8. Determined by ^{1}H NMR.