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TETRAHEDRON: *ASYMMETRY*

Polyfunctionalized pyrrolidinones via the coupling of N,N-disubstituted β-amino esters with ethyl glyoxalate

Dawei Ma * and Jiqing Jiang

State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, PR China

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Abstract

N,N-Disubstituted amino esters were prepared by stereoselective conjugate addition of (S)- or (R)-lithium *N*-benzyl-*N*-α-methylbenzylamide to α,β-unsaturated esters. The couplings of the formed esters with ethyl glyoxalate followed by hydrogenation afforded 5-alkyl-4-carboethoxy-3-hydroxy-pyrrolidinones stereoselectively.
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Owing to their role as intermediates for synthesizing more complex biologically important molecules, optically active polyfunctionalized pyrrolidinones have received considerable attention in the past two decades.[1,2] Those methodologies that can lead to chiral pyrrolidinone with polysubstituted functional groups stereoselectively, are still a goal pursued by synthetic chemists.[1–4] Recently, it was reported that the lithium amides **1** derived from (S)- or (R)-*N*-benzyl-*N*-α-methylbenzylamine could add to certain enoates to give **3** or **6** (Scheme 1) with very high diastereoisomeric excess.[5] Treatment of addition products **3** with LDA followed by quenching the generated anion with a suitable aldehyde produced the aldol condensation products **4**.[6] The diastereoselectivity of this aldol condensation could be improved by using trimethyl borate as an additive.[6,7] Stimulated by these results, we felt that if we used ethyl glyoxalate as an electrophile, the aldol condensation products **4** could spontaneously amidate to form the corresponding chiral pyrrolidinones after deprotection of the amine group. The results of investigations thus undertaken are reported herein.

As outlined in Scheme 1, we prepared **3a** (R=n-Pr, R′=Me) according to a known procedure,[5] which was treated with 3 eq of LDA and the generated anion was trapped with ethyl glyoxalate at −78°C to give the coupling products in 75% yield. The major isomer could be isolated as a crude product (>95% purity) by column chromatography and the ratio of the major isomer over the other isomers is about 4:1. However, using trimethyl borate as an additive before the addition of ethyl glyoxalate, as reported by Yamamoto,[6a] improved coupling yield (92%) and diastereoselectivity was observed (major isomer:other isomers∼7:1). After the separation, the major isomer was directly hydrogenated under the catalysis of

* Corresponding author. E-mail: madw@pub.sioc.ac.cn

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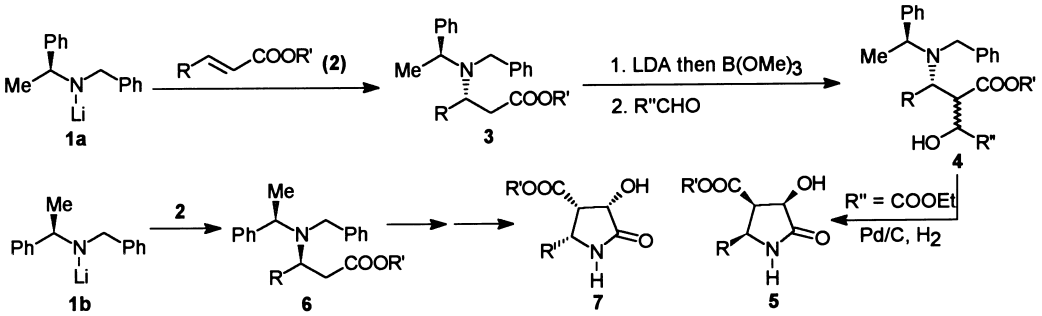


Scheme 1.

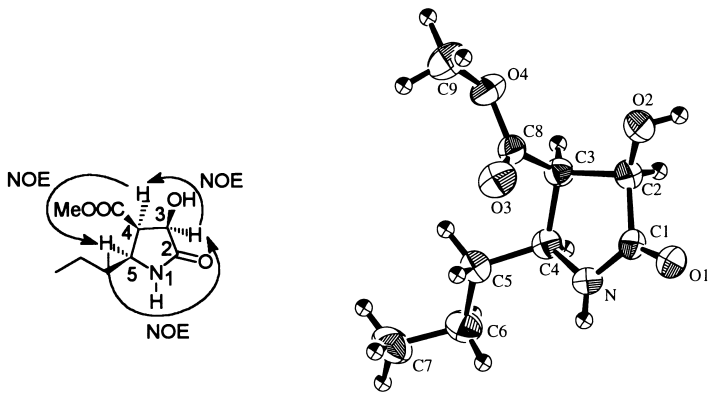
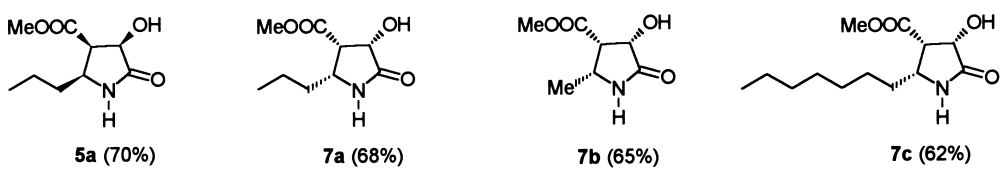


Fig. 1. NOE correlations and X-ray crystal structure of **5a**

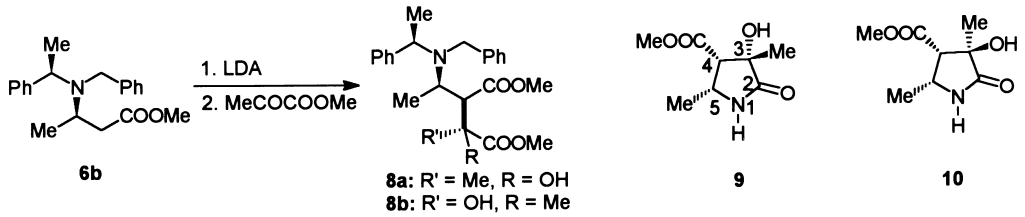
Pd/C. When no more hydrogen was taken in, **5a** was obtained in 82~90% yield after a simple column chromatography. The stereochemistry of the newly created stereogenic centers in **5a** was established by its NOSEY spectrum in which the strong NOEs between H-3 and H-4, H-3 and H-5, H-4 and H-5 were observed. This assignment was further confirmed by a single crystal X-ray analysis of **5a** as shown in Fig. 1. Thus we concluded that the stereochemistry of **5a** is of the (5S,4R,3R)-configuration, which implies that the major isomer in the coupling of **3a** with ethyl glyoxalate should have the (2R,3R,4S)-configuration. This result is consistent with that reported by Yamamoto.[6] We also synthesized other chiral pyrrolidinones **7** with a (5R,4S,3S)-configuration by employing **1b** as a nucleophilic reagent in the first step. The overall yield for preparing each compound from **3** or **6** is indicated in parentheses (Scheme 2). The stereostructure for each compound was confirmed by its NOESY spectrum.



Scheme 2.

To check if α-keto esters are suitable for the present methodology, methyl pyruvate was used as an electrophilic agent to trap the anion derived from **6b** (R=R′=Me). It was found that two crude major isomers **8a** and **8b** could be isolated by column chromatography in 78% total yield. The ratio is about 1.2:1 and no obvious improvement was obtained by employing trimethyl borate as an additive. Without further purification, the two isomers were hydrogenated under the action of Pd/C to give cyclization

products **9** (80%) and **10** (88%) respectively (Scheme 3). The stereochemistry for each compound was assigned by their NOESY spectra. Marked NOEs were observed between H-4 and H-5, H-4 and the 3-methyl group in **9**, while in the NOESY spectrum of **10**, only marked NOE between H-4 and H-5 was noticed.



Scheme 3.

In conclusion, we developed a new method for preparing chiral polyfunctioned pyrrolidinones through the conjugate addition/aldol condensation/deprotection/cyclization approach. Either hydroxy groups or two carbonyl groups in the compounds **5**, **7**, **9** and **10** could be further transformed to give other functional groups and thereby providing the attractive intermediates for synthesizing many natural products. It is obvious that many pyrrolizidine alkaloids[8] such as (−)-isoretronecanol,[9] petasinine,[10] tussilagine and isotussilagine[11] could be synthesized by this methodology. Also, the pyrrolidinone **5a** may serve as a potential intermediate for synthesizing plakoridine A,[12] a tyramine-containing pyrrolidine alkaloid from the Okinawan marine sponge possessing antitumor activity.

1. Experimental section

1.1. General procedures

IR spectra were measured on a Schimadzu 440 spectrometer. ^{1}H NMR spectra were recorded with TMS as an internal strandard on a Brucker AM-300 spectrometer, or a Brucker DRX-400 spectrometer. MS spectra were determined on a Finnigan 4201 spectrometer. Optical rotations were obtained on a Perkin–Elmer 241 Autopol polarimeter. All the N,N-disubstituted amino esters were prepared by following standard procedures[5] and gave satisfactory spectral data. THF was distilled from a deep blue ketyl prior to use. All other solvents were reagent grade quality and used as received. Na_2SO_4 was used as the drying agent in all workup procedures. All reactions were carried out in flame-dried glassware under a nitrogen atmosphere unless otherwise stated.

*1.2. (3R,4R,5S)-3-Hydroxy-4-carbmethoxy-5-n-propylpyrrolidinone **5a***

To a stirring solution of **2a** (4.07 mmol) in 50 mL of THF was added LDA (1 N, 12.2 mmol) dropwise at −78°C. After stirring for 1 h, trimethyl borate (12.2 mmol) was added and the mixture stirred for a further 30 min. After a solution of ethyl glyoxalate (8.1 mmol) in 5 mL of THF was added dropwise at −78°C, the temperature was maintained for 1 h. The reaction was quenched by adding saturated NH_4Cl and the mixture was extracted with ethyl acetate (3×60 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), and dried over Na_2SO_4. After removal of solvent via a rotavapor, the crude product was chromatographed (silica gel, 1:8 ethyl acetate:petroleum ether as eluent) to afford 1.44 g (80% yield) of **4a** ((2R,3R,4S)-isomer), together with other unidentified isomers (0.21g, 12% yield). Without further purification, the product **4a** (~95% purity) was dissolved in 50 mL of methanol and 150

mg of Pd/C was added. The mixture was stirred vigorously under a hydrogen atmosphere at atmospheric pressure until no more hydrogen was taken in. After filtering off the catalyst the filtrate was concentrated and the residual oil was purified by column chromatography eluting with 1:50 methanol:ethyl acetate to afford **5a** in 87% yield. $[\alpha]_D^{25}=-18$ (*c* 1, MeOH); IR (film) 3234, 2951, 1735, 1697, 1651, 1203 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 4.73 (d, *J*=7.5 Hz, 1H), 3.89 (m, 1H), 3.79 (s, 3H), 3.67 (dd, *J*=7.5, 5.7 Hz, 1H), 1.80–1.45 (m, 4H), 1.13 (t, *J*=6.5 Hz, 3H); MS m/z 202 (M^++H^+), 170, 158, 129, 103, 70; HRMS calcd for $C_9H_{15}NO_4$: 201.100; found: 201.100.

*1.3. X-Ray study of **5a***

A single crystal was obtained from methanol at 0°C. A prismatic crystal having approximate dimensions of 0.20×0.20×0.30 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC7R diffractometer with graphite monochromated Mo-Kα radiation and a 12 kW rotating anode generator. Of the 1402 reflections collected, 1267 were unique (R_{int}=0.008). The crystal belongs to a monoclinic space group P21, with *a*=5.097(2), *b*=8.255(2), *c*=12.219(2) Å, β=92.72(2)°, *V*=513.6(2) $Å^3$, *Z*=2, d_c=1.30 g/cm^3, μ=1.0 cm^{-1}. As shown in Fig. 1, because it is known that the stereochemistry for **3a** is the (S)-form, the absolute configuration for C3 and C4 in **5a** should be (R) and the (R)-form respectively.

*1.4. (3S,4S,5R)-3-Hydroxy-4-carbmethoxy-5-n-propylpyrrolidinone **7a***

Overall yield=68% from **6a** (R=n-Pr, R′=Me). $[\alpha]_D^{25}=+10.7$ (*c* 1, MeOH); IR (film) 3234, 2951, 1735, 1695, 1651, 1203 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 4.72 (d, *J*=7.6 Hz, 1H), 3.91 (m, 1H), 3.86 (s, 3H), 3.67 (dd, *J*=7.5, 5.7 Hz), 1.75–1.56 (m, 4H), 1.13 (t, *J*=7.2 Hz, 3H); MS m/z 202 (M^++H^+), 183, 170, 129, 103, 70; HRMS calcd for $C_9H_{15}NO_4$: 201.100; found: 201.097.

*1.5. (3S,4S,5R)-3-Hydroxy-4-carbmethoxy-5-methylpyrrolidinone **7b***

Overall yield=65% from **6b** (R=R′=Me). $[\alpha]_D^{25}=+39.5$ (*c* 1, MeOH); IR (film) 3308, 2928, 1741, 1699, 1652, 1134 cm^{-1}; ^1H NMR (300 MHz, CD_3SOCD_3) δ 4.34 (d, *J*=7.6 Hz, 1H), 3.74 (m, 1H), 3.63 (s, 3H), 3.38 (m, 1H), 1.12 (d, *J*=7.6 Hz, 3H); MS m/z 174 (M^++H^+), 142, 101, 71, 44; HRMS calcd for $C_7H_{11}NO_4$: 173.069; found: 173.068.

*1.6. (3S,4S,5R)-3-Hydroxy-4-carbmethoxy-5-n-heptylpyrrolidinone **7c***

Overall yield=62% from **6c** (R=n-C_7H_{15}, R′=Me). $[\alpha]_D^{25}=+19$ (*c* 1, $CHCl_3$); IR (film) 3280, 2928, 1741, 1699, 1652, 1134 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.59 (br s, 1H), 4.52 (m, 1H), 3.74 (m, 4H), 3.52 (m, 1H), 1.51–1.21 (m, 12H), 1.12 (t, *J*=6.1 Hz, 3H); MS m/z 258 (M^++H^+), 226, 214, 198, 185, 158, 130, 103, 70, 43; HRMS calcd for $C_{13}H_{23}NO_4$: 257.163; found: 257.162.

*1.7. (3S,4S,5R)-3-Hydroxy-3-methyl-4-carbmethoxy-5-methylpyrrolidinone **9** and (3R,4S,5R)-3-hydroxy-3-methyl-4-carbmethoxy-5-methylpyrrolidinone **10***

A mixture of **6b** (3.31 g, 10.6 mmol) in 150 mL of THF was cooled to −78°C. To this solution LDA (1 M, 16 mol) was added dropwise and stirring was then continued for 1 h at the same temperature. After a solution of methyl pyruvate (1.63 g, 16 mmol) in 10 mL of THF was added dropwise at −78°C, the

mixture was stirred for 45 min. The reaction was quenched by adding saturated NH_4Cl solution and the mixture was extracted with EtOAc (3×100 mL). The combined organic layers were washed with water and brine respectively and dried over Na_2SO_4. After removing the solvent, the residual oil was loaded onto a column of silica gel and eluted with 1:8 ethyl acetate:petroleum ether to afford 1.90 g (43% yield) of **8a** and 1.51 g (35% yield) of **8b**, which were hydrogenated directly according to the procedure for preparing **5a** respectively to afford **9** (80% yield) and **10** (88% yield).

9: $[\alpha]_D^{25}$=+67.5 (*c* 1, MeOH); IR (film) 3319, 3177, 1742, 1703, 1656, 1203, 1174 cm^{-1}; ^1H NMR (300 MHz, CD_3SOCD_3) δ 7.81 (br s, 1H), 5.34 (br s, 1H), 3.70 (m, 1H), 3.58 (s, 3H), 3.01 (d, *J*=6.2 Hz, 1H), 1.28 (s, 3H), 1.13 (d, *J*=6.5 Hz, 3H); MS m/z 188 (M^++H^+), 170, 156, 116, 100, 85, 69, 43. HRMS calcd for $C_8H_{13}NO_4$: 187.085; found: 187.086.

10: $[\alpha]_D^{25}$=+112.5 (*c* 1, MeOH); IR (film) 3291, 3217, 1733, 1683, 1657, 1246 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 4.38 (m, 1H), 3.92 (s, 3H), 3.38 (d, *J*=6.7 Hz, 1H), 1.60 (s, 1H), 1.49 (d, *J*=6.5 Hz, 3H); MS m/z 188 (M^++H^+), 170, 156, 116, 101, 85, 69, 44; HRMS calcd for $C_8H_{13}NO_4$: 187.085; found: 187.086

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