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Synthesis, resolution and absolute configuration of *trans* 4,5-diphenyl-pyrrolidin-2-one: a possible chiral auxiliary

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Abstract—β-Lactam (±)-*N*-benzyl-4-phenyl-azetidin-2-one *rac*-**6a** was converted into the γ-lactam (±)-*trans*-4,5-diphenyl-pyrrolidin-2-one *rac*-**5** which was resolved via the preparation of diastereomers with *N*-phthalyl-L-alanine chloride or D-alanine chloride and its absolute configuration was determined by X-ray crystallographic analysis. This heterocycle has potential as a chiral γ-lactam in asymmetric induction due to the steric effects of its phenyl groups.

1. Introduction

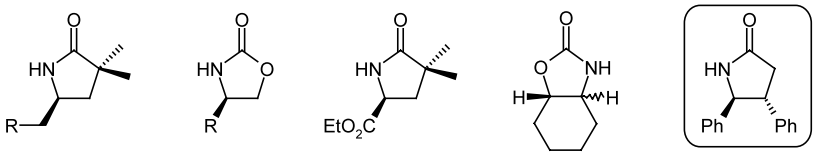
γ-Lactams have potential to act as chiral auxiliaries in the asymmetric synthesis of many kinds of products.[1] Some of the most explored chiral γ-lactams are the pyrrolidinones **1a**–**d** developed by Davies et al.[2] that have some advantages over the classic oxazolidinones described by Evans[3] **2a**–**b** or by Sibi et al. **2c**.[4] Another related auxiliary is pyroglutamate **3** developed by Ezquerra et al.[5] which has been shown to control the stereoselectivity of *N*-acyl fragments in aldol condensations or in conjugate additions. Further application was reported by Juaristi et al.[6] in *cis*- and *trans*-hexahydrobenzoxazolidinones **4** to control the stereoselectivity in *N*-acyl fragments in alkylation and aldol reactions. The chiral γ-lactam-**5** also might be considered as an effective chiral auxiliary for asymmetric synthesis in which the asymmetric induction may be realized by the steric effects of phenyl groups (Fig. 1).

Among the methods available to synthesize **5**, the methodologies based on employing an acyclic compound to form the heterocycle are very common; In particular, cyclization of γ-amino acids[7] or γ-amino esters[8] has been used frequently. In this context, we describe an alternative route for the preparation of the racemic *trans* 4,5-diphenyl-pyrrolidin-2-one **5**.[9] We subsequently developed a process for the resolution of the racemate and determined the configuration of this heterocycle.

2. Results and discussion

2.1. Synthesis of γ-lactam (±)-*trans* 4,5-diphenyl-pyrrolidin-2-one *rac*-5

The γ-lactam *rac*-**5** was prepared from β-lactam (±)-*N*-benzyl-4-phenyl-azetidin-2-one *rac*-**6a** by lateral chain incorporation in a ring expansion process[10] with 1.1



1a R = $OCPh_3$
1b R = OTBMS
1c R = H
1d R = Me

2a R = $CH(CH_3)_2$
2b R = CH_2Ph
2c R = $CH(Ph)_2$

3

4

5

Figure 1.

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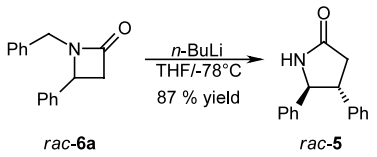


Scheme 1.

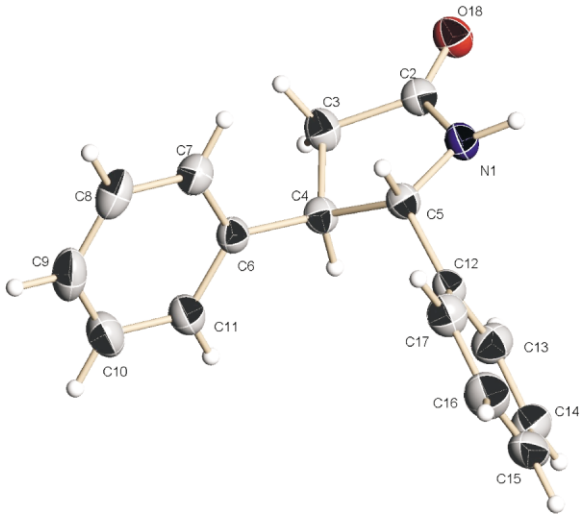


Figure 2. X-Ray diffraction study of (±)-*trans*-4,5-diphenyl-pyrrolidin-2-one *rac*-**5**.

mol equiv. of *n*-butyllithium in THF at −78°C under a nitrogen atmosphere in 87% yield. The expansion reaction was carried out from −78°C to room temperature during 1 h giving 72% yield, while at rt the expansion proceeded in only 55% yield. We obtained exclusively the *trans* product and did not observe the formation of the *cis* isomer by ^{1}H NMR (Scheme 1).

An X-ray crystallographic analysis was performed with a suitable crystal of *rac*-**5**, and a view of the solid-state structure is shown in Fig. 2. The heterocyclic ring is rather flat and has the five atoms approximately in a plane. The most interesting feature of the crystal structure is that the phenyl groups are located in a *trans* arrangement in pseudo equatorial positions. The practical consequences are significant, since one of the phenyl groups can be regarded as sterically hindered for attack on one face in the course of stereoselective alkylation, acylation and aldol condensation similar to the classic oxazolidinones by Evans.[3]

We have demonstrated that the expansion mechanism proposed[11] in Fig. 3 proceeds via benzylic anion intermediate **I** (see Section 2.1.1) and, because of ring strain, a rearrangement to give the imine anion **II** (which is stabilized by resonance, see Section 2.1.2) occurs to release the ring strain of the small four-membered ring.[12] Finally, a Michael type reaction occurs for the ring closure to give the more stable *trans* γ-lactam *rac*-**5** (see Section 2.1.3).

2.1.1. Benzylic anion I formation. The β-lactam *rac*-**6a** was treated with *n*-BuLi in THF at −78°C (expansion conditions), after 1 min pivaloyl chloride was added to obtain *rac*-**7** with one pivaloyl group in the benzylic position in 83% yield (Scheme 2). This experiment indicates that the formation of the benzylic anion **I**[9] can be considered as the first step in the expansion mechanism.

2.1.2. Imine anion II formation. To probe the second step and to explore the effect of substitution at the C(4) position in the starting material, we carried out the expansion reaction under the same conditions with β-lactams *rac*-**6b** and **6c** (Scheme 3).

With these substrates no reaction has been observed probably because of the absence of any resonance as in **II** (induced by the phenyl group) assisting the stabilizing of the carbanion intermediate **IV**.

2.1.3. Ring strain as the 'driving force'. Finally, to probe if the ring strain in the β-lactam *rac*-**6a** is the driving force for the rearrangement, we prepared the analogous heterocycle *N*-benzyl γ-lactam *rac*-**8**. *rac*-**8** was treated

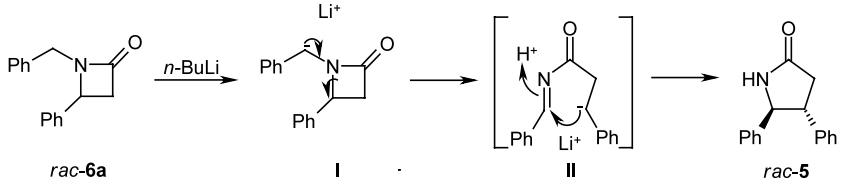
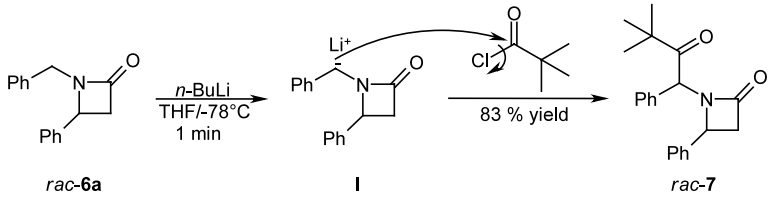
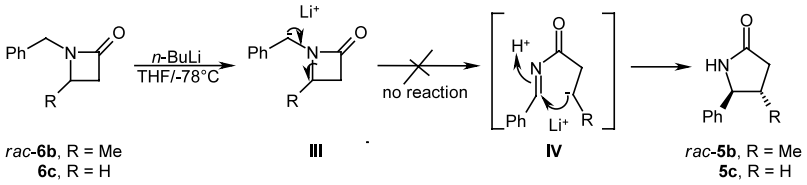


Figure 3. Reaction mechanism for the ring expansion.

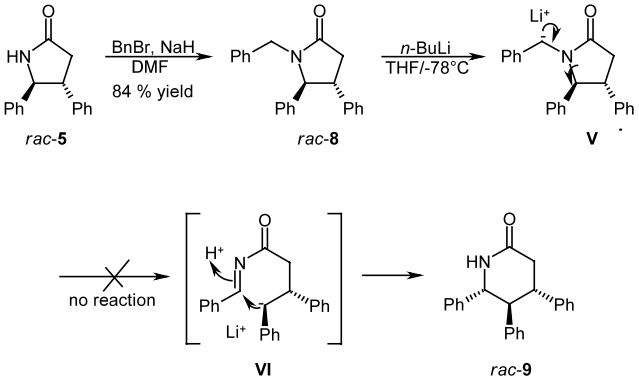


Scheme 2.



Scheme 3.

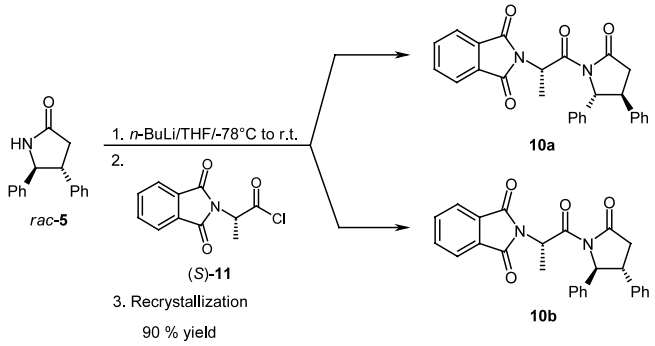
with *n*-BuLi following the established procedure for the expansion conditions. Also in these cases, no detectable conversion of the reactant was observed. We interpret this observation as the five member heterocycle ring now being stable, thus not promoting the expansion. This observation is in agreement with our mechanistic explanation (Scheme 4).



Scheme 4.

2.2. γ-Lactam-5, resolution and absolute configuration determination

The resolution was achieved by the preparation of the diastereomers **10a** and **10b** via condensation between the γ-lactam anion, formed with *n*-BuLi from −78°C to rt, and *N*-phthalyl-L-alanine chloride (*S*)-**11** as the resoluting agent. Separation of the diastereomers was accomplished by fractional crystallization from hexane/AcOEt (Scheme 5).



Scheme 5.

The assignment of the absolute configuration of the main products was achieved by X-ray diffraction analysis with the diastereomer **10a** (Fig. 4). In this way, we were able to determine the relative configuration *S* at C(4) and *R* at C(5) in the heterocyclic system for diastereomer **10a**, and consequently the opposite configuration for diastereomer **10b** [*R* at C(4) and *S* at C(5)].

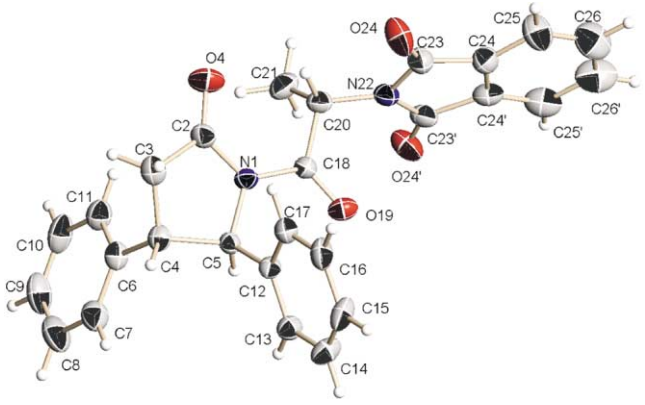
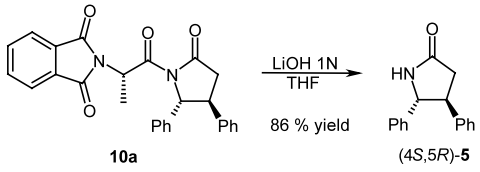


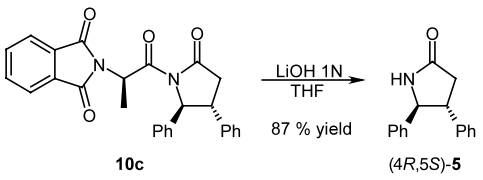
Figure 4. Structure and solid-state conformation for (4*S*,5*R*,α*S*)-**10a**.

Finally, as shown in Scheme 6, conversion of diastereoisomer **10a** to the enantiomerically pure γ-lactam (4*S*,5*R*)-**5** was completed by hydrolysis with LiOH in 86% yield.



Scheme 6.

Enantiomerically pure (4*R*,5*S*)-**5** γ-lactam was obtained from **10c** by the use of *N*-phthalyl-D-alanine chloride as the resolving agent (Scheme 7) since attempts to recrystallize diastereomer **10b** had failed.



Scheme 7.

3. Conclusions

In this paper, we present a new method for the preparation of enantiomerically pure γ-lactams (4*S*,5*R*)-**5** and (4*R*,5*S*)-**5**. The interest for these γ-lactams as chiral auxiliaries is given by their potential to be used in the intramolecular protective formation of γ-amino acids. Further studies to explore these γ-lactams as new chiral auxiliaries in the synthesis of amino acids are in progress.

4. Experimental

4.1. General

TLC: Merck-DC-F_{254} plates; detection by UV light. Flash column chromatography:[13] Merck silica gel (0.040–0.063 mm). Mp: Mel-Temp apparatus; not corrected. Optical rotations were determined in a Perkin–Elmer 241 polarimeter at the sodium D-line. ^{1}H NMR spectra: Varian Oxford 400 MHz, Varian Mercury 200 MHz. ^{13}C NMR spectra: Varian Oxford 100 MHz, Varian Mercury 50 MHz. Chemical shifts (δ) in ppm downfield from the integral TMS reference; the coupling constants (J) in Hz. X-Ray: APEX-Bruker diffractometer. The structures were solved by direct methods using the program SHELXS.[14]

Flasks, stirring bars and hypodermic needles used for the generation and reactions of organolithiums were dried for 12 h at 120°C and allowed to cool in a desiccator over anhydrous $CaSO_4$. Anhydrous solvents were obtained by distillation from benzophenone ketyl.[15] The *n*-BuLi employed was titrated according to the method of Juaristi et al.[16]

4.2. General procedure for the ring expansion

Under N_2 a dry flask fitted with magnetic stirrer and a solution of the appropriate β-lactam[17] in anhydrous THF was cooled to −78°C before the slow addition of 1.1 mol equiv. of *n*-BuLi in hexane (2.4 M). The resulting solution was stirred at −78°C for 30 min and then quenched with a saturated ammonium chloride solution and then with 10 mL of water. The aqueous phase was extracted with three 10 mL portions of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to give the crude product. The crude material was recrystallized from mixtures of MeOH and CH_2Cl_2 to yield the pure γ-lactam.

4.2.1. (±)-*trans* 4,5-Diphenyl-pyrrolidin-2-one *rac*-5. 87% yield as white crystals, mp 215–218°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (dd, $J_{gem}=16.5$ Hz, $J_{anti}=8.8$ Hz, 1H), 2.87 (dd, $J_{gem}=16.5$ Hz, $J_{syn}=9.9$ Hz, 1H), 3.40 (ddd, $J_{anti}=8.8$ Hz, $J_{syn}=9.9$ Hz, $^3J=7.7$ Hz, 1H), 4.70 (d, $^3J=7.7$ Hz, 1H), 6.36 (s, 1H), 7.15–7.35 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.2, 51.0, 65.3, 126.5, 127.1, 127.7, 127.9, 128.7, 128.8, 141.4, 141.8, 176.1. MS, m/z 237 (M^+). X-Ray crystallographic structure in Fig. 2.[18]

4.2.2. (±)-1-(3,3-Dimethyl-2-oxo-1-phenyl-butyl)-4-phenyl-azetidin-2-one *rac*-7. The general procedure was followed for ring expansion, and after 1 min 1.1 mol equiv. of pivaloyl chloride was added. Purification of the crude product by flash chromatography (hex/AcOEt, 10:0→0:10) afforded 83% yield of *rac*-**7**. Colorless crystals, mp 77–79°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.33 (s, 9H), 2.78 (dd, $J_{gem}=17.6$ Hz, $J_{anti}=6.2$ Hz, 1H), 3.13 (dd, $J_{gem}=17.6$ Hz, $J_{syn}=8.4$ Hz, 1H), 3.38 (ddd, $J_{anti}=6.2$ Hz, $J_{syn}=8.4$ Hz, $^4J=5.2$ Hz, 1H), 5.30 (d, $^4J=5.2$ Hz, 1H), 7.10–7.35 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.3, 39.9, 42.2, 46.5, 70.1, 125.4, 126.2, 127.0, 127.6, 127.9, 128.2, 129.0, 129.1, 140.9, 141.2, 173.4, 180.9.

4.3. (±)-1-Benzyl-*trans*-4,5-diphenyl-pyrrolidin-2-one *rac*-8

A mixture 1:1 of solvents THF/DMF was added to the *trans*-4,5-diphenyl-pyrrolidin-2-one (*rac*-**5**) at 0°C in an ice-water bath. This suspension was treated with 2.2 mol equiv. of NaH and 1.1 mol equiv. of benzyl bromide. The ice-water bath was removed and stirring continued at room temperature over night. The mixture was filtered, evaporated and purified by flash chromatography (hex/AcOEt, 10:0→0:10) afforded 84% yield of *rac*-**8**. Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$), δ 2.71 (dd, $J_{gem}=17.1$ Hz, $J_{anti}=7.8$ Hz, 1H), 3.06 (dd, $J_{gem}=17.1$ Hz, $J_{syn}=9.1$ Hz, 1H), 3.34 (ddd, $J_{anti}=7.8$ Hz, $J_{syn}=9.1$ Hz, $^3J=6.1$ Hz, 1H), 4.30 (d, $^3J=6.1$ Hz, 1H), 3.51, 5.20 (AB, $J=J'=14.3$, 2H), 6.95–7.45 (m, 15H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 38.6, 44.8, 47.7, 69.5, 127.1, 127.2, 127.2, 127.7, 128.4, 128.7, 128.8, 128.9, 129.1, 136.2, 139.4, 141.7, 174.2.

4.4. General procedure for the γ-lactam-5 resolution

A solution of *rac*-**5** in THF was cooled to −78°C before slowly adding 1.1 mol equiv. of *n*-butyllithium in hexane (2.4 M). The resulting solution was stirred at −78°C for 10 min and further at room temperature for 15 min, and treated successively with the resolution agent (*N*-phthalyl-L-alanine or D-alanine chloride).[19] The mixture was stirred at the same temperature for 1 h and treated with saturated ammonium chloride solution and then with water. The aqueous phase was extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), filtered and evaporated to give the crude product. Purification of the crude product was accomplished by flash chromatography (hexane/AcOEt) and then by recrystallization from hexane/AcOEt yielding the corresponding diastereomer.

4.4.1. 2-[1(*S*)-Methyl-2-oxo-2-(5-oxo-2(*R*),3(*S*)-diphenyl-pyrrolidin-1-yl)-ethyl]-isoindole-1,3-dione 10a. 90% Yield; mp 188–189°C; $[\alpha]_D^{25}=-61.9$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87 (d, $J=7.2$ Hz, 3H), 2.76 (dd, $J_{gem}=18.4$ Hz, $J_{anti}=2.4$ Hz, 1H), 3.22 (dd, $J_{gem}=18.4$ Hz, $J_{syn}=8.8$ Hz, 1H), 3.41 (ddd, $J_{anti}=2.4$ Hz, $J_{syn}=8.8$ Hz, $^3J=2.4$ Hz, 1H), 5.32 (d, $^3J=2.4$ Hz, 1H), 6.02 (*c*, 1H), 7.16–7.40 (m, 10H), 7.68 (dd, $J=2.8$ Hz, $J'=5.6$ Hz, 2H), 7.82 (dd, $J=2.8$ Hz, $J'=5.6$ Hz,

2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.9, 38.7, 45.9, 51.2, 68.9, 123.5, 125.1, 126.5, 127.9, 128.0, 129.2, 129.5, 132.2, 134.1, 140.1, 142.3, 168.0, 170.7, 174.9. X-Ray crystallographic structure in Fig. 4.[18]

4.4.2. 2-[1(*R*)-Methyl-2-oxo-2-(5-oxo-2(*S*),3(*R*)-diphenyl-pyrrolidin-1-yl)-ethyl]-isoindole-1,3-dione 10c. 80% Yield; mp 188–189°C; $[\alpha]_D^{25}=+61.4$ (*c* 1.1, $CHCl_3$).

4.5. Procedure for remotion of the resolution agent

To the appropriate diastereomer in THF was added at 0°C an excess of 1N LiOH solution under stirring for 2 h. The resulting mixture was concentrated at reduced pressure and purified by column chromatography (hex/AcOEt 50:50→0:10) to give the product as a white solid.

4.5.1. *trans*-(4*S*,5*R*)-Diphenyl-pyrrolidin-2-one, (4*S*,5*R*)-5. 86% Yield. White solid, mp 104–106°C. $[\alpha]_D^{25}=-150.1$ (*c* 1.1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (dd, $J_{gem}=16.8$ Hz, $J_{anti}=9.2$ Hz, 1H), 2.87 (dd, $J_{gem}=16.8$ Hz, $J_{syn}=8.8$ Hz, 1H), 3.39 (ddd, $J_{anti}=9.2$ Hz, $J_{syn}=8.8$ Hz, $^3J=7.2$ Hz, 1H), 4.69 (d, $^3J=7.2$ Hz, 1H), 6.48 (s, 1H), 7.15–7.38 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.6, 51.3, 66.2, 126.1, 127.5, 128.4, 129.0, 140.8, 141.0, 176.7.

4.5.2. *trans*-(4*R*,5*S*)-Diphenyl-pyrrolidin-2-one, (4*R*,5*S*)-5. 87% Yield. $[\alpha]_D^{25}=+149.2$ (*c* 1.1, MeOH).

4.6. Determination of absolute configuration of γ-lactams

Configurations in the C(4) and C(5) positions of (4*S*,5*R*)- and (4*R*,5*S*)-γ-lactams-**5** were determined relative to (*S*) stereogenic center of L-alanine or (*R*) for D-alanine mediated X-ray diffraction.

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