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Stereoselective synthesis of (1*R*,4*R*)-*N*-acyl-2-oxa-5-aza-bicyclo[2.2.1]heptan-3-ones via mesoionic compounds. An improved synthesis of *cis*-4-hydroxy-D-proline

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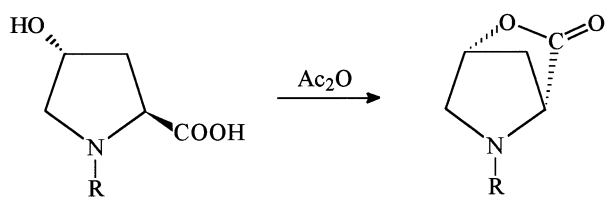
Abstract—We report an asymmetric synthesis of (1*R*,4*R*)-*N*-acyl-2-oxa-5-aza-bicyclo[2.2.1]heptan-3-ones, starting from the inexpensive and commercially available *trans*-4-hydroxy-L-proline and achieved by treating *N*-acyl-*trans*-4-hydroxy-L-prolines with acetic anhydride. The formation of intermediate mesoionic compounds may explain the formation of *N*-acyl-2-oxa-5-aza-bicyclo[2.2.1]heptan-3-ones with (*R*)-absolute configuration at C(4). Acidic cleavage of these lactones readily affords *N*-acyl-*cis*-4-hydroxy-D-prolines or *cis*-4-hydroxy-D-proline in good yields.

1. Introduction

Continuing with our studies into the reactivity and synthetic usefulness of mesoionic compounds derived from the cyclodehydration of cyclic *N*-acyl α-amino acids,[1–4] we proposed a short and very simple synthesis of (1*R*,4*R*)-*N*-acyl-2-oxa-5-aza-bicyclo[2.2.1]heptan-3-ones. While trying to prepare (2*S*,4*R*)-4-acetyloxy-*N*-benzoylproline[3] and (2*S*,4*R*)-4-acetyloxy-*N*-acetylproline,[5] we found that under certain experimental conditions the reaction of (2*S*,4*R*)-*N*-acyl-4-hydroxyprolines **1a** and **1b** with acetic anhydride afforded (1*R*,4*R*)-*N*-acyl-2-oxa-5-aza-bicyclo[2.2.1]heptan-3-ones **2a** and **2b**, respectively (Scheme 1). This aroused our interest because the lactones were obtained with (*R*)-absolute configuration at C(4), thus showing that inversion of configuration at C(2) of the proline ring had occurred.

A survey of the literature showed that *N*-acetyl-2-oxa-5-aza-bicyclo[2.2.1]heptan-3-one[6] **2a** and *N*-benzoyl-2-oxa-5-aza-bicyclo[2.2.1]heptan-3-one[7] **2b** have always been synthesized with (1*S*,4*S*)-absolute configuration: i.e. in the enantiomeric form with respect to our lactones. The reported methods of synthesis[6,7] made use of *trans*-4-hydroxy-L-proline **1c** as the starting material (Scheme 2): the key step in these procedures was the inversion of configuration at C(4) of the proline ring by means of an internal S_N2 nucleophilic displacement of the activated hydroxyl group (route A), or isomerization through C(4) oxidation/reduction (route B).

Various *N*-substituted 2-oxa-5-aza-bicyclo[2.2.1]heptan-3-ones[8] (with (1*S*,4*S*)-absolute configuration) have also been prepared using these routes. Some (1*R*,4*R*)-*N*-substituted lactones are known,[9] but they were obtained by means of a lactonization reaction of substrates already having the (*R*)-configuration at the two stereocenters.



1a,b,c **2a,b**

R = (a) COMe
(b) COPh
(c) H

Scheme 1.

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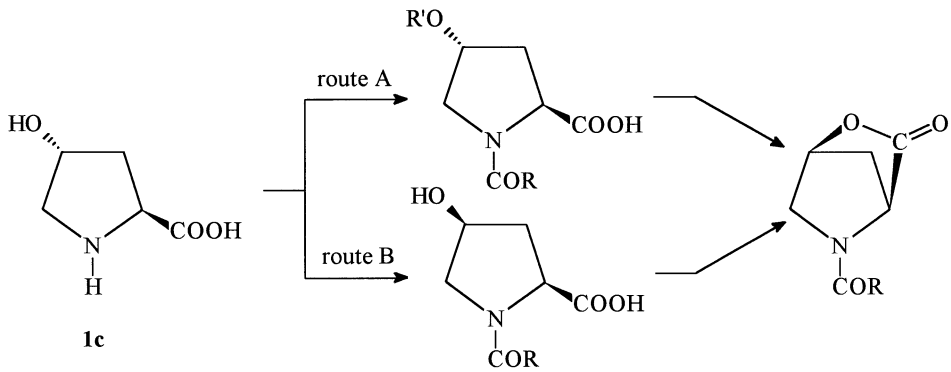


Scheme 2.

To the best of our knowledge, only one publication[10] has reported a (1*R*,4*R*)-*N*-aroyl-2-oxa-5-aza-bicyclo[2.2.1]heptan-3-one obtained as a by-product during a cycloaddition reaction between a *trans*-*N*-aroyl-4-hydroxy-L-proline and dimethyl aceytylenedicarboxylate in the presence of acetic anhydride at 120°C, but no explanation for the result was proposed. We therefore decided to study the reaction of (2*S*,4*R*)-*N*-acyl-4-hydroxyprolines **1a** and **1b** with acetic anhydride in an attempt to explain the formation of the lactone enantiomers. We also determined the experimental conditions necessary to open the lactonic ring and obtain the *cis*-4-hydroxy-D-proline or the corresponding *N*-acyl derivatives.

L-Proline and the *cis*- and *trans*-4-hydroxy-L-prolines are naturally found in peptides or secondary metabolites. Their great importance in determining the preferred peptide conformation and the formation of their secondary structures is well known, so it is always of interest to study the influence of non-natural prolines in peptide derivatives. To this end, it is useful to have a simple and advantageous synthesis of *cis*-4-hydroxy-D-proline because, although commercially available, it is very expensive. Furthermore, obtaining the known *N*-acetyl-*cis*-4-hydroxy-D-proline[11] or the unknown *N*-benzoyl derivative directly from the corresponding lactones gives better yields.

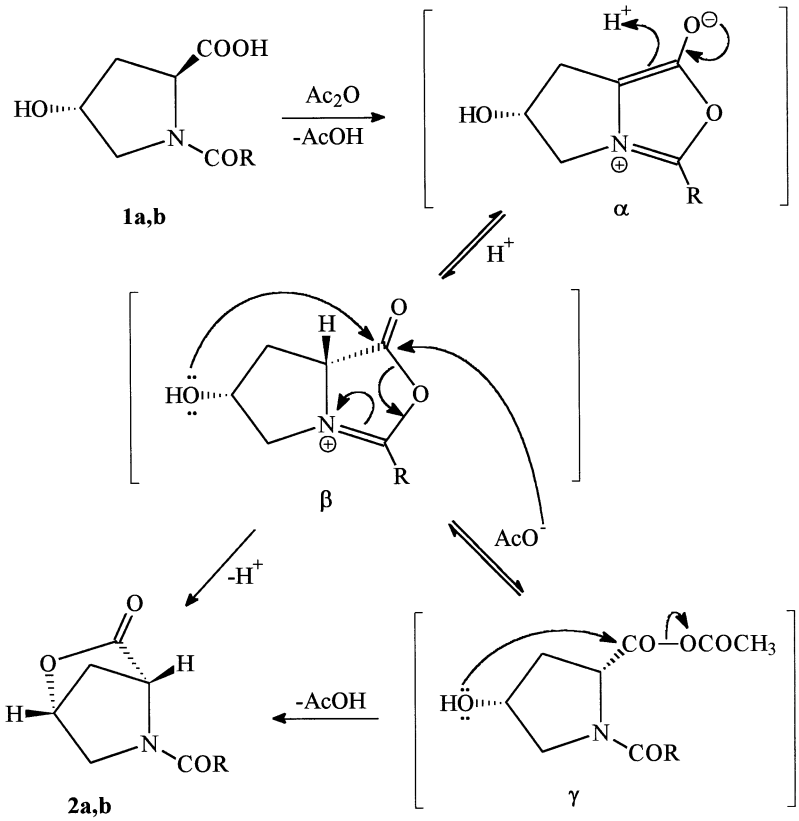
2. Results and discussion

We tested the reactions of the commercial (2*S*,4*R*)-*N*-acetyl-4-hydroxyproline **1a**, (2*S*,4*R*)-*N*-benzoyl-4-hydroxyproline[7a] **1b** and *trans*-4-hydroxy-L-proline **1c** with acetic anhydride under various experimental conditions in order to determine which were better (Scheme 1 and Table 1). The product obtained with **1c** was the same (1*R*,4*R*)-*N*-acetyl-2-oxa-5-aza-bicyclo[2.2.1]heptan-3-one **2a** deriving from *N*-acetylation of the substrate and subsequent reaction with acetic anhydride. Given the low solubility of the prolines in apolar solvents, the reactions were performed in acetic anhydride at temperatures ranging from room temperature to reflux. Some experiments completed in toluene afforded very poor yields. As shown in Table 1, the reaction is influenced by temperature and the *N*-substitution. The best yields were generally obtained at 90°C in times of 7–16 h. The yields were lower when the reaction was completed in refluxing acetic anhydride, which is probably because of the instability of the products under these conditions. At room temperature, the reaction time was very long but the yields were good except in the case of the *trans* isomer **1c**: this could be due to the more difficult *N*-acetylation reaction at room temperature. When the hydroxyproline was *N*-unsubstituted (substrate **1c**), the yields were always lower than in the case of the *N*-acetyl substrate **1a**. The yields were best when the hydroxyproline was *N*-benzoyl substituted (substrate **1b**), and nearly the same at every temperature. The obtained lactones **2a** and **2b** were enantiomerically pure.

In order to explain these experimental results and the observed stereochemical behavior, we considered the reaction mechanism shown in Scheme 3. The *trans* relative configuration between the hydroxyl and carboxyl groups in the proline substrates did not allow direct dehydration to the lactones derivatives. On the contrary, in acetic anhydride, the presence of an *N*-acyl group allowed the formation of the corresponding intermediate bicyclic mesoionic compounds **α**. Their subsequent protonation by means of the forming acetic acid was induced by the existing stereocenter and occurred from the less hindered side (opposite the hydroxyl group). Finally, the intermediates **β** gave lactones **2** through the direct intramolecular attack of the

Table 1.

Substrate	*T* (°C)	*t* (h)	Product	Yield (%)
1a	rt	72	**2a**	80
1a	60	7	**2a**	67
1a	60	16	**2a**	72
1a	90	7	**2a**	82
1a	135	7	**2a**	62
1b	rt	72	**2b**	82
1b	60	7	**2b**	80
1b	90	7	**2b**	84
1c	rt	72	**2a**	12
1c	60	16	**2a**	55
1c	90	7	**2a**	48
1c	90	16	**2a**	64
1c	135	9	**2a**	39



Scheme 3.

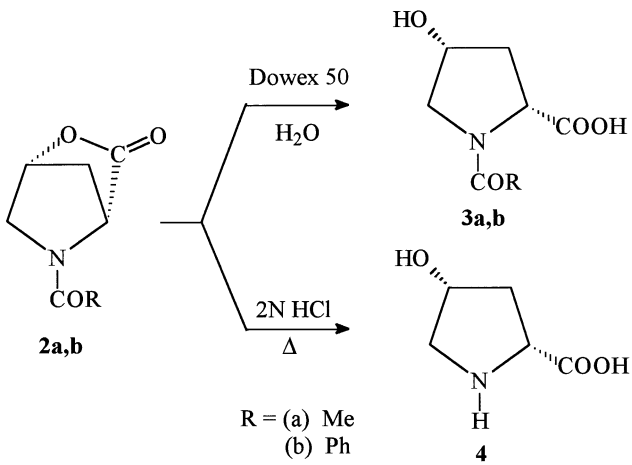
hydroxylic oxygen on the carbonyl carbon, or through the intermediate mixed anhydrides γ deriving from the attack of the acetate anion on the same carbonyl group. We have already observed complete asymmetric induction from the C(4) stereogenic carbon of the *trans*-4-hydroxy-L-proline[3] on the newly forming C(2) stereocenter. In this way, the lactones **2** were obtained with inversion of configuration at C(2) of the proline substrate and retention of configuration at C(4), i.e. with the (1*R*,4*R*)-absolute configuration. Obviously, this method can only be used to synthesize *N*-acyl substituted lactones because the presence of the *N*-acyl group is fundamental for mesoionic formation.

We subsequently considered the possibility of opening these lactones in order to obtain *N*-acyl-*cis*-4-hydroxy-D-prolines **3a** and **3b** (Scheme 4). The known *N*-acetyl compound **3a**[11] was prepared in good yields (76–83%) by *N*-acetylating *cis*-4-hydroxy-D-proline;[11,12] this was obtained in moderate yields (42–56%) by epimerizing the *trans*-4-hydroxy-L-proline. Compound **3a** was prepared from *trans*-4-hydroxy-L-proline in total yields ranging from 32 to 46%. Compounds **2a** and **2b** afforded (2*R*,4*R*)-*N*-acyl-4-hydroxy-prolines **3a** and **3b** in good yields (80–85%, respectively) when treated with a strong cationic resin (Dowex 50) in water at room temperature. In this way, the total yields increased to 66–71%, respectively.

On the other hand, heating **2a** in aqueous hydrochloric acid afforded the *cis*-4-hydroxy-D-proline **4** in 75% yield. The completion of the two steps (acetylation and acid hydrolysis), without isolating the intermediate lactone, made it possible to obtain the *cis*-4-hydroxy-D-proline **4** in 76% total yield from the *trans*-4-hydroxy-L-proline **1c**. This result represents an improvement on the reported method[11a] in which C(2) epimerization was only 75% and the total yield was 42%.

3. Conclusion

In conclusion, our method allows the synthesis of (1*R*,4*R*)-*N*-acyl-2-oxa-5-aza-bicyclo[2.2.1]heptan-3-ones



Scheme 4.

starting from *trans*-4-hydroxy-L-prolines. The formation of the intermediate mesoionic compounds leads to inversion of configuration at C(2) of the proline ring, and thus affords the (1*R*,4*R*)-lactones. In this way, it is possible to synthesize both enantiomers from the same available compound by changing the synthetic scheme. Subsequent hydrolysis makes it possible to obtain *cis*-4-hydroxy-D-proline or its *N*-acyl derivatives in better yields than those previously reported, depending on the experimental conditions.

4. Experimental

4.1. General methods

Melting points were determined using a Büchi apparatus and are uncorrected. All the ^{1}H NMR spectra were recorded by means of a Bruker AC 300 spectrometer. Chemical shifts (δ) are given in ppm relative to TMS and the coupling constants (J) are reported in Hz. Optical rotations were measured using a Perkin–Elmer 241 spectropolarimeter. Compounds **1a** and **1c** were commercial products; **1b** was prepared according to the method of Portoghese.[7a]

4.2. General procedure for the preparation of (1*R*,4*R*)-*N*-acyl-2-oxa-5-aza-bicyclo[2.2.1]heptan-3-ones 2a and 2b

A mixture of **1a** or **1b** (15 mmol) and acetic anhydride (25 mL) was stirred and heated at 90°C for 7 h, under nitrogen. After evaporation of the solvent, the residue was taken up in dichloromethane (50 mL) and the solution was washed with cold water. The organic phase was dried (Na_2SO_4) and the solvent evaporated off. The products were recrystallized and identified by means of analytical and spectroscopic data.

4.2.1. Compound 2a. White solid, mp 95–98°C (iPrOH); $[\alpha]_D^{20}=-60.5$ (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.97 (dd, $J=11.45$, 1.72, 0.35H, H-7), 2.05 (s, 1.05H, CH_3), 2.11 (dd, $J=10.82$, 1.79, 0.65H, H-7), 2.19 (s, 1.95H, CH_3), 2.26 (d, $J=10.5$, 0.35H, H-7), 2.32 (dd, $J=10.85$, 1.10, 0.65H, H-7), 3.53 (d, $J=10.08$, 0.35H, H-6), 3.60,3.62 (2s, 1.3H, H-6+H-6), 3.69 (d, $J=10.06$, 0.35H, H-6), 4.45 (s, 0.65H, H-4), 5.09 (s, 0.35H, H-4), 5.16 (s, 1H, H-1). IR (KBr): 1786, 1650 cm^{-1}. Anal. calcd for $C_7H_9NO_3$: C, 54.19; H, 5.81; N, 9.03. Found: C, 54.03; H, 5.75; N, 8.92%.

4.2.2. Compound 2b. White solid, mp 134–135°C (iPrOH); $[\alpha]_D^{20}=-92.75$ (c 1.00, EtOH); ^{1}H NMR ($CDCl_3$): δ 2.03 (dd, $J=10.88$, 1.29, 1H, H-7), 2.22 (d, $J=10.92$, 1H, H-7), 3.63 (d, $J=9.93$, 1H, H-6), 3.81 (d, $J=10.68$, 1H, H-6), 4.51 (s, 1H, H-4), 5.16 (s, 1H, H-1), 7.37–7.48 (m, 3H, arom.), 7.57 (d, $J=7.64$, 2H, arom.). IR (KBr): 1796, 1628 cm^{-1}. Anal. calcd for $C_{12}H_{11}NO_3$: C, 66.36; H, 5.07; N, 6.45. Found: C, 66.23; H, 5.05; N, 6.37%.

4.3. General procedure for the preparation of (2*R*,4*R*)-*N*-acyl-4-hydroxy-prolines 3a and 3b

To a solution of **2a or 2b** (5 mmol) in water/acetone = 1/1 (20 mL) Dowex 50×8 resin (1.5 g) was added in portions and the mixture was stirred at room temperature until reaction was complete (about 48 h). The mixture was filtered and the filtrate concentrated. The products were recrystallized and identified by means of analytical and spectroscopic data.

4.3.1. Compound 3a. White solid, mp 142–143°C (iPrOH); $[\alpha]_D^{20}=+88.2$ (c 1.00, H_2O); [lit.:[11b] mp 145.5–147°C; $[\alpha]_D^{22}=+91.00$ (c 9.70, H_2O)]; ^{1}H NMR (D_2O): δ 2.1 (s, 3H, CH_3), 2.15–2.58 (m, 2H, 2H-3), 3.42–3.89 (m, 2H, H-5), 4.49–4.64 (m, 1H, H-2), 4.7–4.87 (m, 1H, H-4). Anal. calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.36; N, 8.09. Found: C, 48.45; H, 6.30; N, 8.01%.

4.3.2. Compound 3b. White solid, mp 138–140°C ($CHCl_3$); $[\alpha]_D^{20}=+71.25$ (c 1.00, EtOH); ^{1}H NMR ($CDCl_3$): δ 2.27 (m, 2H, 2H-3), 3.62 (m, 2H, H-5), 4.35 (broad s, 1H, H-2), 4.69 (dd, $J=8.62$, 2.81, 1H, H-4), 7.25–7.51 (m, 5H, arom.). Anal. calcd for $C_{12}H_{13}NO_4$: C, 61.28; H, 5.53; N, 5.96. Found: C, 61.23; H, 5.45; N, 5.87%.

4.4. Hydrolysis of 2a to *cis*-4-hydroxy-D-proline 4

A stirred mixture of **2a** (0.775 g, 5 mmol) and 2N aqueous HCl (3 mL) was heated under gentle reflux temperature for 2 h. The solution was decolorized with charcoal while hot, filtered through Celite, and then neutralized to pH 6 with 5N NaOH (1 mL). The product was purified by adsorption on Dowex 50×8 ion-exchange resin: the resin was washed with distilled water until chloride ions disappear, then eluted with 5 M NH_4OH. Product **4** was obtained as a white solid in 75% yield. Mp 254–255°C (decomp.) ($EtOH/H_2O=2/1$); $[\alpha]_D^{20}=+58.27$ (c 2.00, H_2O); [lit.:[11b] mp 252–257°C; $[\alpha]_D^{22}=+60.3$ (c 2.60, H_2O)]; ^{1}H NMR (D_2O): δ 2.08, 2.13 (2m, 1H, H-3), 2.37 (ddd, $J=14.4$, 10.2, 4.6, 1H, H-3), 3.20 (dd, $J=12.46$, 3.95, 1H, H-5), 3.30 (dd, $J=12.48$, 1.54, 1H, H-5), 4.10 (dd, $J=10.41$, 388, 1H, H-2), 4.40 (m, 1H, H-4). Anal. calcd for $C_5H_9NO_3$: C, 45.80; H, 6.87; N, 10.69. Found: C, 45.65; H, 6.70; N, 10.51%.

4.5. Synthesis of *cis*-4-hydroxy-D-proline 4 from *trans*-4-hydroxy-L-proline 1c

A stirred mixture of **1c** (6.55 g, 50 mmol) and acetic anhydride (40 mL) was heated at 90°C for 16 h under nitrogen. The solution was evaporated under reduced pressure to give a thick oil that was dissolved in 2N aqueous HCl (30 mL). The solution was heated under reflux for 2 h, then decolorized with charcoal while hot, filtered through Celite and neutralized to pH 6 with 5N NaOH (10 mL). Product **4** was purified as described above and was obtained with the same purity in a total yield of 76%.

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