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β-KETOESTERS DERIVED FROM PYROGLUTAMIC ACID: NEW ENTRY TO HYDROXYLATED PYRROLIZIDINONES

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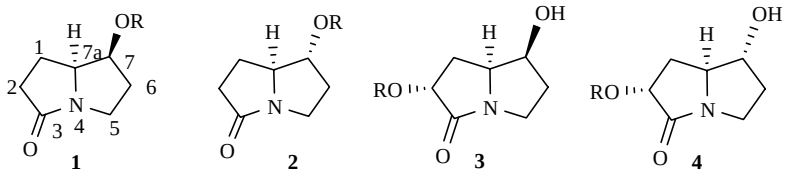
Abstract – Four hydroxylated pyrrolizidinones have been obtained from β-ketoesters derived from L-pyroglutamic acid or 4-(*R*)-hydroxy-L-pyroglutamic acid. The asymmetric hydrogenations, in the presence of $BinapRuBr_2$ catalysts, of such β-ketoesters bearing pyrrolidinones proceeded with high diastereomeric excesses leaving to a complete control of the absolute configuration at the C7 hydroxylated carbon atom of the azabicycles.

INTRODUCTION

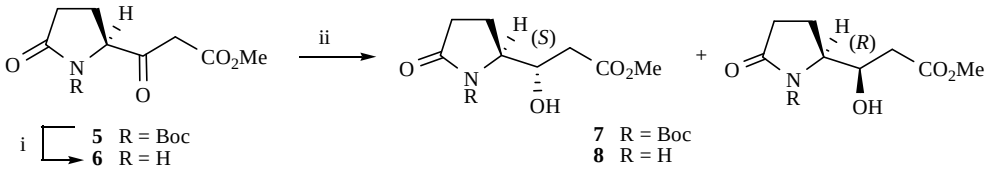
Functionalized pyrrolizidinones are the subject of significant research activity, mainly due to their behaviour as rigid dipeptide mimics.[1] Moreover, they may be used in organic synthesis as intermediates for the preparation of plant-derived alkaloids.[2] The mono- and dihydroxylated pyrrolizidinones **1**, **2** and **3**, **4** respectively, could be such interesting precursors for these structures and could be obtained from the β-ketoesters bearing a pyrrolidinone. These will be prepared by homologation of L-pyroglutamic and 4-(*R*)-hydroxy-L-pyroglutamic acids[3] using the Masamune procedure.[4] The key step of the syntheses is a catalytic hydrogenation of the β-ketoesters[5,6] which will allow the control of the absolute configuration of the C7 hydroxylated asymmetric carbon atom. To our knowledge, that reaction has not been described in the literature for β-ketoesters bearing a lactam moiety. The absolute configurations of the C7a and/or C2 asymmetric carbons of the azabicycles would be brought respectively by the use of L-pyroglutamic acid and 4-(*R*)-hydroxy-L-pyroglutamic acid. The results of the hydrogenation step and the preparations of the hydroxylated pyrrolizidinones **1**, **2**, **3** and **4** are reported in the present note.



1 **2** **3** **4**

RESULTS AND DISCUSSION

We first studied the reactivity of the β-ketoesters derived from L-pyroglutamic acid bearing the protected or the free amide, respectively **5** and **6** (Scheme 1). For comparison with the catalytic hydrogenations, we had introduced them in a step of classical reduction in the presence of sodium borohydride. The reduction of the substrate **5** has led to a mixture of degradation products resulting from the ring-opening of the *N*-protected pyrrolidinone. The same reaction applied to the compound **6** has given the expected β-hydroxyesters **8** with a yield of 91%, as an inseparable mixture of the two epimers by silica gel chromatography. The low diastereoselectivity (*S*/*R* = 47/53) has been determined by NMR spectroscopy.



Scheme 1. i) TFA, 97%; ii) H_2, MeOH, 2% Ru Catalyst, 55°C, 40 h.

The first experiments of catalytic hydrogenation[7] were run under atmospheric pressure, at 55 °C during 40 h using the *N*-Boc substrate **5** (Table 1, entries 1 and 2). Complete deprotection of the carbamate was observed under these conditions and the β-hydroxyester **8** was obtained with good yields and excellent diastereoselectivities. The β-hydroxyester (*R*)-**8** was isolated as a single diastereomer with a yield of 89% using (*S*)-BinapRuBr$_2$ as catalyst. With the antipode complex as catalyst, the compound (*S*)-**8** was obtained with a yield of 97% and a diastereoisomeric excess of 94%. Then the catalytic hydrogenation step was run under higher pressure (entries 3 and 4). Under these conditions, the carbamate deprotection was not complete and a mixture of *N*-Boc protected β-hydroxyester **7** and β-hydroxyester **8** was obtained. The diastereomeric ratios of the β-hydroxyesters (*R*)-**8** and (*S*)-**8** were comparable at those obtained precedently. Surprisingly, a decrease of the diastereoselectivity was observed for the *N*-Boc protected β-hydroxyester **7**: (*R*)-**7** and (*S*)-**7** were obtained with diastereomeric excesses of 72% and 76% respectively. The β-ketoester **6** bearing the free amide was hydrogenated under atmospheric and high pressures (entries 5-8). In all cases, the β-hydroxyesters **8** were obtained with good to quantitative yields. Under high pressure, the diastereoselectivity increased for (*R*)-**8** which was obtained with a

diastereomeric excess of 96% (entry 7). A diastereomeric excess of 94% was measured for (*S*)-**8** even at atmospheric and high pressure (entries 6 and 8).

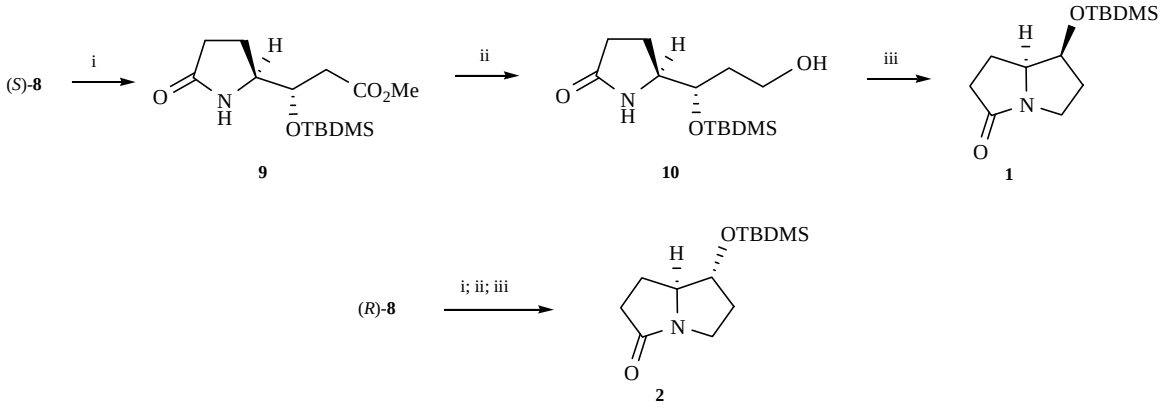
Table 1. Catalytic hydrogenation of **5** and **6**

Entry	Substrate	Catalyst[a]	P (atm)	Product	Yield (%)	d.r.[b] (*S*/*R*)
1	**5**	(*S*)-BinapRuBr$_2$	1	**8**	89	> 1/99
2	**5**	(*R*)- BinapRuBr$_2$	1	**8**	97	97/3
3	**5**	(*S*)-BinapRuBr$_2$	98	**7**	27	14/86
				+ 8	38	9/91
4	**5**	(*R*)- BinapRuBr$_2$	98	**7**	65	88/12
				+ 8	20	95/5
5	**6**	(*S*)- BinapRuBr$_2$	1	**8**	100	11/89
6	**6**	(*R*)- BinapRuBr$_2$	1	**8**	98	93/7
7	**6**	(*S*)-BinapRuBr$_2$	98	**8**	92	2/98
8	**6**	(*R*)- BinapRuBr$_2$	98	**8**	92	93/7

[a] Conditions: H_2, MeOH, 55°C, 40 h.

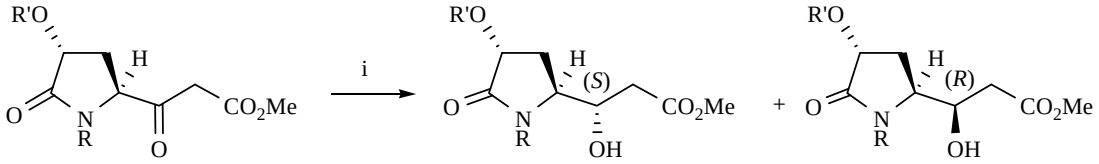
[b] d.r. determined by NMR spectroscopy.

The compounds (*S*)-**8** and (*R*)-**8** have been introduced respectively in the ways of formation of the azabicycles **1** and **2** protected as their *O*-*tert*-butyldimethylsilyl ethers (Scheme 2). The protection of the hydroxyl group of the β-hydroxyester (*S*)-**8** using *tert*-butyldimethylsilyl chloride produced the corresponding silyl ether **9** with a yield of 75%. The selective reduction of the methyl ester has been possible with a large excess of sodium borohydride, leading to **10**. This last one has been cyclised into **1** *via* a two-steps sequence, consisting in the activation of the primary alcohol with mesyl chloride, followed by a cyclisation of the intermediate sulfonate in the presence of potassium *tert*-butylate (65% in two steps). Spectral data and optical rotation were in agreement with the one of the literature.[8] The same sequence applied to (*R*)-**8** has led to the epimer **2**[9] with similar yields.



Scheme 2. i) TBDMSCl, DMF, Imid., 75%; ii) $NaBH_4$, MeOH, 92%; iii) MsCl, Et_3N, DCM then *t*BuOK, THF, 65%.

In a second part, we have studied the catalytic hydrogenation of the β-ketoesters derived from 4-(*R*)-hydroxy-L-pyroglutamic acid, protected or not on the amide and/or hydroxyl function: **11**, **12** and **13** (Scheme 3). The results are summarised in the Table 2.



11 R = Boc; R' = TBDMS
12 R = Boc; R' = H
13 R,R' = H

14 R = Boc; R' = TBDMS
15 R = Boc; R' = H
16 R,R' = H

Scheme 3. i) H_2, MeOH, 2% Ru Catalyst, 50°C.

The hydrogenation of the fully protected substrate **11** in the presence of the (*R*)-BinapRuBr$_2$ catalyst gave a complexed product mixture (entry 1): competitive reactions of deprotection or elimination of the *tert*-butyldimethylsilyl ether were observed. The β-hydroxyester **14** was isolated with a very low yield of 12% and without diastereoisomeric excess. The use of the Ikariya catalyst (*R*)-[(RuClBinap)$_2$(μ-Cl)$_3$][NH_2Et_2][10] leaded to the β-hydroxyester (*S*)-**14** as the single diastereoisomer with a yield of 30% (entry 2). For the hydrogenation of **12** when the (*S*)-Binap ruthenium catalyst was used only degradation products have been observed. The use of the (*R*)-BinapRuBr$_2$ complex led to the β-hydroxyester **15** as a single diastereoisomer with a low yield of 17%. Deprotection of the carbamate occurred simultaneously and the β-hydroxyester **16** was isolated with a yield of 33% and a diastereomeric ratio of 90/10 in favor of the (*S*)-diasteroisomer (entry 3). These observations were in concordance with the results of Ohtake *et al.*,[11] who had shown the importance of an unprotected γ-amino moiety in the reaction of hydrogenation of the β-ketoester bearing 4-hydroxypyrrolidine. Finally, better results were obtained using the fully deprotected β-ketoester **13** as substrate in the hydrogenation step. The reactions were run at atmospheric pressure and 55 °C in the presence of (*S*)- or (*R*)-BinapRuBr$_2$ catalysts to give respectively the β-hydroxyesters (*R*)-**16** and (*S*)-**16** with good to quantitative yields and high diastereomeric ratios. We noticed that the hydrogenation reaction proceeded slowly when the (*S*)-BinapRuBr$_2$ complex was used and the β-hydroxyester **16** was isolated with an acceptable yield of 82% after 80 h.

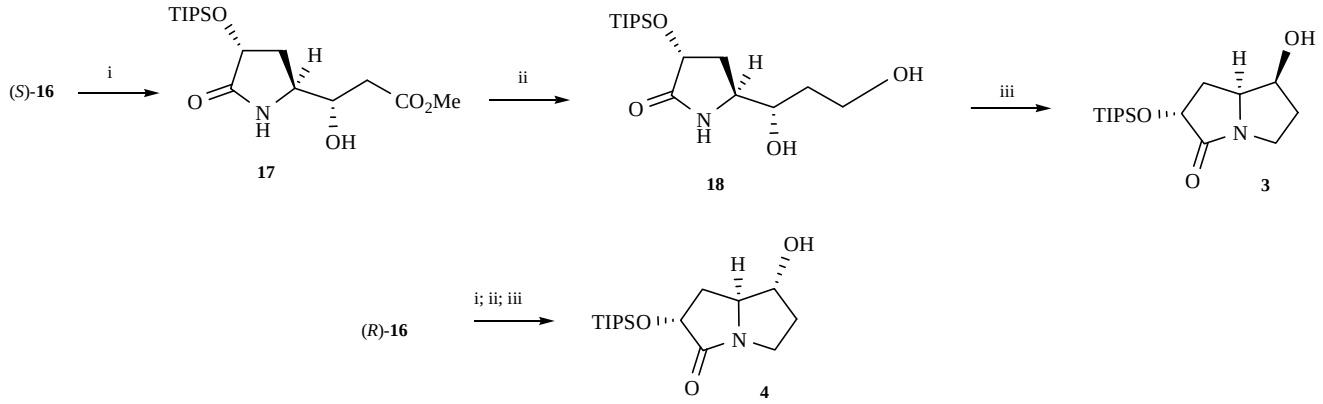
Table 2. Catalytic hydrogenation of **11**, **12** and **13**

Entry	Substrate	Catalyst[a]	Time (h)	Product	Yield (%)	d.r.[b] (*S*/*R*)
1	**11**	(*R*)-BinapRuBr$_2$	24	**14**	12	50/50
2	**11**	(*R*)-[(RuClBinap)$_2$(μ-Cl)$_3$][NH_2Et_2]	16	**14**	30	99/1
3	**12**	(*R*)-BinapRuBr$_2$	40	**15**	17	99/1
				+ 16	33	90/10
4	**13**	(*S*)- BinapRuBr$_2$	80	**16**	82	7/93
5	**13**	(*R*)- BinapRuBr$_2$	24	**16**	98	94/6

[a] Conditions: H_2, MeOH, atmospheric pressure, 55°C.

[b] d.r. determined by NMR spectroscopy.

We have then carried on the synthesis of the bicycle **3**, starting from the β-hydroxyester (*S*)-**16** (Scheme 4). Its reaction with 1 equivalent of triisopropylsilyl chloride in DMF in presence of imidazole has given exclusively the mono-silyl ether **17**, without any trace of silylation of the hydroxyl group of the β-hydroxyester. The reduction of the ester function afforded the diol **18** with a yield of 85%. Selective activation of the primary hydroxyl group, and treatment under basic conditions gave the bicyclic compound **3**[12] with a yield of 43%. The same sequence applied to (*R*)-**16** has led to the bicycle **4**.[13]



Scheme 4. i) TIPSCl, DMF, Imid., 76%; ii) $NaBH_4$, MeOH, 85%; iii) TsCl, DCM/pyr: 2/1 then *t*BuOK, THF, 43%.

In conclusion, both diastereoisomers of the β-hydroxyesters **8** and **16** have been obtained with very good yields and diastereoselectivities. The stereoselective catalytic hydrogenation of the β-hydroxyester **5** derived from the *N*-Boc-L-pyroglutamic acid proceeded simultaneously with the cleavage of the *tert*-butyl carbamate at atmospheric pressure. The 7-hydroxypyrrolizidinones **1** and **2** protected as *tert*-butyldimethylsilyl ether were obtained easily in a three-steps sequence from the both diastereomers of **8**. The 2,7-dihydroxypyrrolizidinones **3** and **4** monoprotected as triisopropylsilyl ether at C2 were

synthetized respectively from the β-ketoesters (*S*)-**16** and (*R*)-**16** derived from 4-(*R*)-hydroxy-L-pyroglutamic acid.

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7. The catalyst was prepared under argon according to the next procedure: To bis-(2-methylallyl)-cycloocta-1,5-diene-ruthenium(II) complex (0.02 equiv.) and (*R*)- or (*S*)-2,2'-bis(diphenylphosphino)-1,1'-binaphtyl (0.02 equiv.) in degazed acetone (1 mL/mmol of catalyst) was added a methanolic solution of hydrogen bromide (0.15-0.18*M*, 0.04 equiv.). The reaction mixture was stirred 30 min. The solvents were evaporated and the β-ketoester (1 mmol) in freshly distilled degazed MeOH (1.7 mL) was cannulated to the catalyst. The reaction mixture was stirred under hydrogen atmosphere (see tables for conditions of pressure, temperature and time). The solvents were evaporated and a purification by column chromatography gave the corresponding β-hydroxyesters.
8. $[\alpha]_D^{25}$ +33 (*c* 0.53, $CHCl_3$) {lit.[2b]: $[\alpha]_D^{25}$ +33 (*c* 1.045, $CHCl_3$)}.
9. (7*R*,7a*S*)-7-[*tert*-Butyldimethylsilyl)oxy]-3-oxopyrrolizidine (**2**): $[\alpha]_D^{25}$ -37 (*c* 0.4, $CHCl_3$). IR (cm^{-1}): 2955.33, 2924.61, 2883.64, 2852.92, 1700.71, 1460.03, 1413.94, 1255.19, 1132.29, 1029.87, 835.28. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 6 H, 2 Me), 0.87 (s, 9 H, *t*Bu), 1.74 (m, 1 H, H-1),

1.93 (m, 1 H, H-6), 2.14-2.42 (m, 3 H, H-1', H-6' and H-2), 2.66 (m, 1 H, H-2'), 3.17 (m, 1 H, H-5), 3.58 (m, 1 H, H-5'), 3.69 (dd, 1 H, *J* = 6.9, 13.9 Hz, H-7a), 3.81 (dd, 1 H, *J* = 6.9, 13.7 Hz, H-7). ^{13}C NMR (75 MHz, $CDCl_3$): δ = -4.81 and -4.70 (Me), 17.91 (CMe_3), 25.08 (C-1), 25.64 (CMe_3), 34.26 (C-2), 35.67 (C-6), 39.84 (C-5), 67.41 (C-7a), 76.59 (C-7), 175.12 (CO). ESI-HMRS: *m/z* calcd for $C_{13}H_{25}NO_2NaSi$ $[M+Na]^+$: 278.1552; found: 278.1556.

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11. N. Ohtake, H. Jona, S. Okada, O. Okamoto, Y. Imai, R. Ushijima, and S. Nakagawa, *Tetrahedron: Asymmetry*, 1997, **8**, 2939.
12. (2*R*,7*S*,7a*S*)-7-Hydroxy-2-triisopropylsilyloxy-3-oxopyrrolizidine (**3**): $[\alpha]_D^{25}$ +2 (*c* 0.5, $CHCl_3$). IR (cm^{-1}): 3652.13, 2976.88, 2934.37, 2867.32, 1714.05, 1443.91, 1382.17, 1123.02, 844.93. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07-1.10 (m, 21 H, 3 *i*Pr), 1.93 (m, 1 H, H-1), 2.05-2.31 (m, 2 H, H-6), 2.41 (m, 1 H, H-1), 3.17 (m, 1 H, H-5), 3.60 (m, 1 H, H-5'), 3.97 (m, 1 H, H-7a), 4.11 (t, 1 H, *J* = 3.3 Hz, H-7), 4.46 (dd, 1 H, *J* = 2.5, 7.3 Hz, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.12, 17.81 and 17.88 (*i*Pr_3), 30.14 (C-1), 36.16 (C-6), 39.32 (C-5), 64.34 (C-7a), 69.34 (C-7), 75.66 (C-2), 174.86 (CO). ESI-HMRS: *m/z* calcd for $C_{16}H_{31}NO_3NaSi$ $[M+Na]^+$: 336.1971; found: 336.1969.
13. (2*R*,7*R*,7a*S*)-7-Hydroxy-2-triisopropylsilyloxy-3-oxopyrrolizidine (**4**): $[\alpha]_D^{25}$ -22 (*c* 0.4, $CHCl_3$). IR (cm^{-1}): 3365.01, 2939.97, 2863.16, 1695.59, 1690.47, 1460.03, 1137.41, 1091.32, 876.24, 676.53.^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.08-1.09 (m, 21 H, 3 *i*Pr), 1.69 (bs, 1 H, OH), 1.84-2.33 (m, 4 H, H-1 and H-6), 3.28 (m, 1 H, H-5), 3.61 (m, 1 H, H-5'), 3.84–4.00 (m, 2 H, H-7 and H-7a), 4.40 (dd, 1 H, *J* = 1.1-1.3, 5.9-6.1 Hz, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.10, 17.79 and 17.88 (*i*Pr_3), 35.59 (C-1 or C-6), 36.87 (C-1 or C-6), 39.98 (C-5), 65.55 (C-7a), 75.90 (C-7 or C-2), 76.02 (C-7 or C-2), 173.66 (CO). ESI-HMRS: *m/z* calcd for $C_{16}H_{31}NO_3NaSi$ $[M+Na]^+$: 336.1971; found: 336.1977.