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DIASTEREOSELECTIVE SYNTHESIS OF CHIRAL METHYL 2-PIPERIDIN-2-YLPROPANOATES

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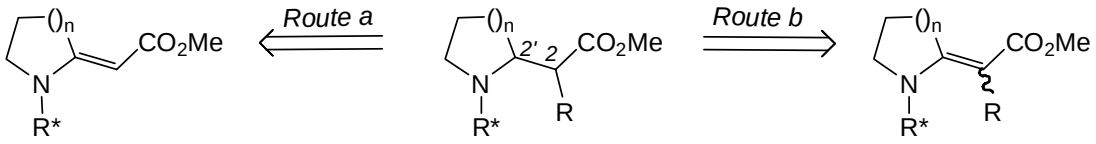
Abstract – We report the synthesis of methyl (2*S*,2'*R*)-2-piperidin-2-ylpropanoate by the diastereoselect ion of the tetrasubtituted double bond of piperidine β-enamino ester (**1**)ive reduct.

INTRODUCTION

As a part of our search towards the preparation of chiral polyfunctional heterocycles, we have been interested in the synthesis of pyrrolidin- and piperidin-2-ylacetates as useful intermediates in the synthesis of alkaloids[1,2] or biologically active compounds.[3] Among the various possible approaches,[4] the asymmetric synthesis of these cyclic β-amino esters may rely on the hydrogenation of the corresponding β-enamino esters bearing a tri- or tetrasubstituted exocyclic double bond, the control of the new stereogenic center(s) being achieved either by chiral catalysis[5] or by asymmetric induction.[6,7,8] In our laboratory, we have developped such an approach based on the diastereoselective reduction of the corresponding β-enamino esters bearing a chiral auxiliary at the nitrogen atom.[2,7,9] In the pyrrolidine series, the creation of two contiguous stereogenic centers C-2 and C-2' of chiral pyrrolidine 2-substituted acetates **I** with a (*S*)-phenylethyl substituted nitrogen atom (Scheme 1, n = 1) was achieved either successively by a reduction/alkylation sequence[9] starting from trisubstitued β-enamino ester **II** (Scheme 1, *route a*, n = 1), or simultaneously by reduction[10] of tetrasubtituted derivatives **III** (Scheme 1, *route b*, n = 1). In the piperidine series, only the reduction/alkylation sequence was studied from **II** (Scheme 1, *route a*, n = 2).[11] As we had recently prepared the unprecedented chiral piperidine β-enamino esters **III** (Scheme 1, n = 2) possessing an unusual (*Z*)-tetrasubstitued double bond,[12] we decided to study the diastereoselective reduction of the latter compound, in order to compare the stereochemical outcome of the two routes for the piperidine derivatives.



II (n = 1,2) **I** (n = 1,2) **III** (n = 1,2)

Scheme 1

Herein, we report the results of this program in the particular case of methyl piperidin-2-ylidene propanoate **(1)** as the starting enamino ester (Figure 1). The reasons for this choice were based on the good results previously obtained on the analogous pyrrolidine.[10]

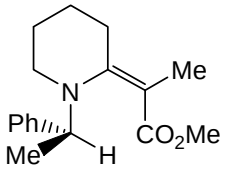


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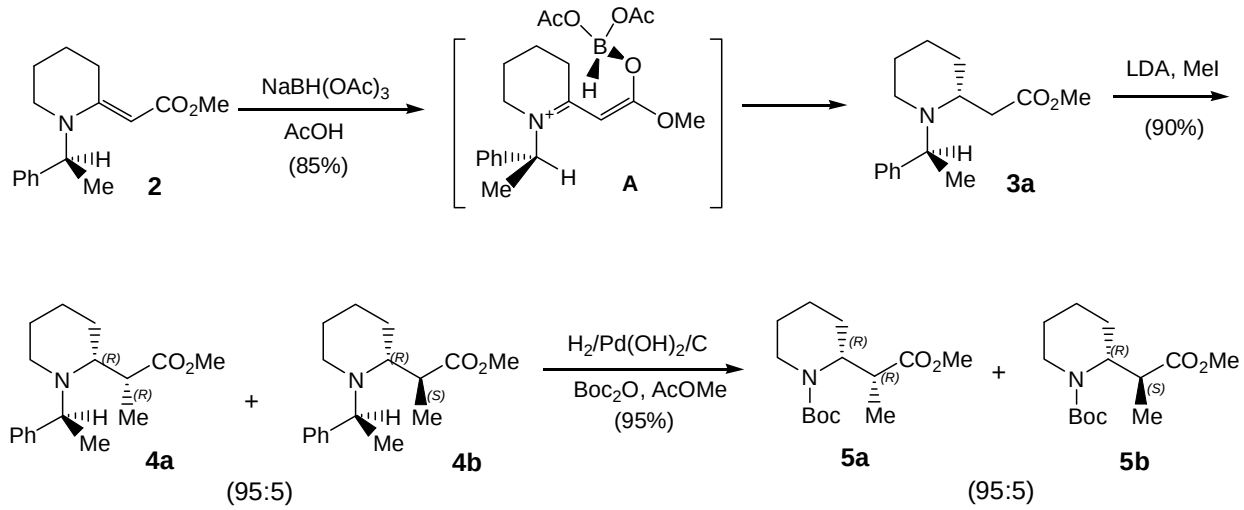
Figure 1

RESULTS AND DISCUSSION

As a preliminary work to allow an easy identification of the reduced compounds, we first prepared methyl 2-piperidin-2-yl propanoate (**4**) according to *route a* (Scheme 1) starting from the β-enamino ester (**2**)[13] (Scheme 2). The reduction of the double bond of **2** was efficiently and stereoselectively achieved by *in situ* generated sodium triacetoxy borohydride in acetic acid[14] to afford to amino ester (**3**) as a 95:5 mixture[15] of two diastereomers. The control of the stereochemistry at the C-2 center could be explained considering the formation of the enol ester-diacetoxy borohydride intermediate (**A**),[14] in which the 1,3-allylic strain is minimized and the hydride ion is transferred from the less hindered face (*Si* face at C-2') anti to the phenyl substituent (Scheme 2). The major isomer (**3a**)[8] was isolated in 85% yield after column chromatography and further subjected to methylation with MeI as briefly reported on analogous compounds.[11,16] In contrast with the conditions usually described in the literature for piperidine acetates,[11,17] we found out that the use of LDA as the base at 0°C smoothly afforded the expected propanoates (**4**) as an unseparable 95:5 mixture[15] of diastereomers and in an excellent 90% overall yield after column chromatography. The major diastereomer (**4a**) was isolated in 73% yield after treatment of the mixture with picric acid, subsequent crystallization of the resulting salt and conversion back to the free base. The absolute stereochemistry of **4a** was assumed to be (2*R*, 2'*R*) as previously reported for analogous compounds.[11] Indeed, X-ray analysis performed on the picric salt of **4a** secured this assignment[18] (Figure 2). Concerning the minor isomer (**4b**), its absolute configuration was consequently attributed to (2*S*, 2'*R*), assuming that no epimerization had occurred at C-2' during the alkylation step.



Scheme 2

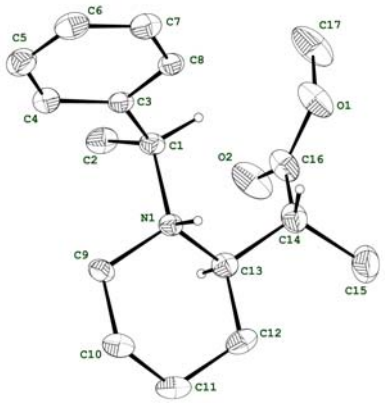
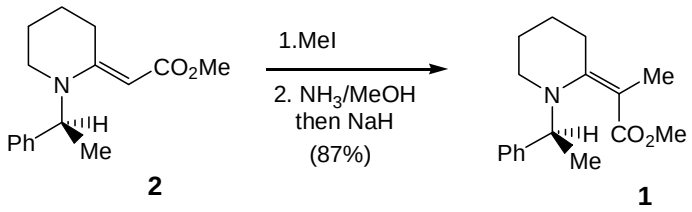


Figure 2. Crystal structure of the picrate of **4a**

These results in hand, we investigated the direct reduction of β-enamino ester (**1**). The stereoselective synthesis of this compound (as the single *Z*-isomer) was achieved as previously reported[12] by reacting enantiopure piperidine enamino ester (**2**)[13] in refluxing methyl iodide followed by the successive treatment with methanolic ammonia and sodium hydride[19] (Scheme 3).



Scheme 3

The reduction of the β-enamino ester (**1**) was first performed using sodium triacetoxy borohydride in acetic acid[14] to yield mainly degradation products of the starting material (about 70% of the crude reaction mixture estimated by GC analysis) along with a 12:81:7 mixture of three diasteromers (**4a**), (**4b**)

and (**4c**) (GC analysis), arising from the chemoselective reduction of the double bond of **1**. This disappointing result prompted us to investigate catalytic hydrogenation of **1**. Reaction carried out under an atmospheric pressure of hydrogen using Pt/C as the catalyst gave rise to four diastereomers (**4a**), (**4b**), (**4c**) and (**4d**) as a 17:64:18:1 mixture as estimated by CG analysis[20] (Scheme 4). Identification of the structure of compounds (**4a**) and (**4b**) was established by co-injection of the above mixture in a gas chromatograph with the compound obtained according to *route a* (Scheme 2), whereas the identification of compounds (**4c**) and (**4d**) will be discussed below. Considering the poor diastereoselectivity obtained under these conditions, we switched to Pd/C as the catalyst. In this case, the reduction of compound (**1**) gave rise to debenzylated products[21] that were readily transformed[7] into their *N*-*tert*-butoxycarbonyl derivatives (**5**) to allow easier purification and identification (Scheme 4). This reaction proceeded diastereoselectively to give two diastereomers (**5**) in a 6:94 ratio as estimated by GC analysis with an achiral column and in 62% overall yield for two steps after column chromatography on silica gel. The major diastereomer of **5** was isolated in 54% yield. Noteworthy, GC analysis on a chiral column showed the presence of three isomers in the initial mixture and of two enantiomers for the isolated major diastereomer. In order to assign the absolute configuration of these compounds, a 95:5 mixture of compounds (**4a**) and (**4b**) stemming from *route a* (Scheme 2) was submitted to debenzylation (H_2, $Pd(OH)_2$/C) followed by *in situ* carbamatation in the presence of Boc_2O.[2] This sequence afforded a 95:5 mixture of enantiopure compounds (2*R*, 2'*R*)-(**5a**) and (2*S*, 2'*R*)-(**5b**) in 96% overall yield (Scheme 2).[22] Gas chromatography experiments on chiral and achiral columns, consisting of a series of injections and co-injections of these different mixtures, showed that the mixture of compounds (**5**) was composed of isomers (**5a**), (**5b**) and *ent*-(**5b**) in a 6:88:6 ratio.[23] Thus, hydrogenation was able to efficiently and diastereoselectively reduce compound (**1**) into methyl 2-piperidin-2-ylpropanoate (2*S*, 2'*R*)-(**5b**), the very same minor isomer obtained according to *route a*. This result showed that this reduction had initially proceeded through through the *syn* favored approach of hydrogen from the less hindered face (*Si* face at C-2') of the conformer of **1** where the 1,3-allylic strain is minimized (Figure 3). Although compound (**5b**) was not obtained enantiomerically pure (e.e. 88%), our approach constitutes the only reported way to access to the (2*S*, 2'*R*) stereochemistry of 2-piperidin-2-ylcarboxylates.

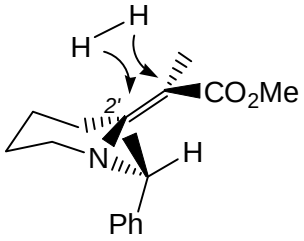
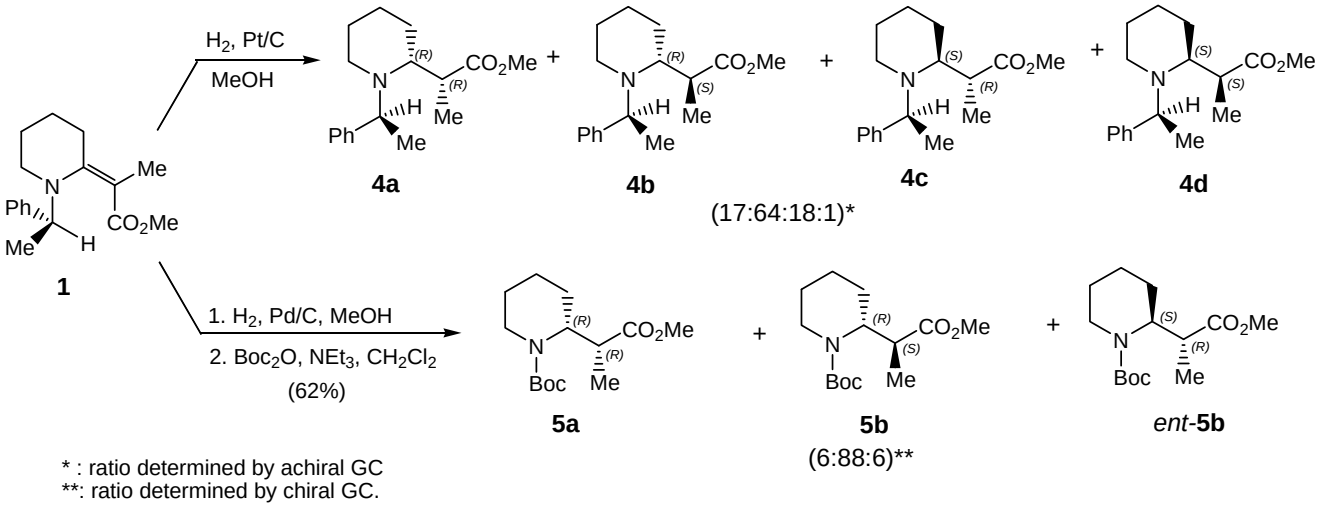


Figure 3. Favored *syn* approach of hydrogen for the reduction of compound (**1**)

Following these results, the (18:62:18:2) mixture of compounds (**4a-d**), stemming from the hydrogenation of **1** in the presence of Pt/C, was also transformed into the corresponding *tert*-butoxycarbonyl derivatives (**5**), as a 18:62:18:2 mixture of compounds (**5a**), (**5b**), *ent*-(**5b**) and *ent*-(**5a**) respectively, according to chiral GC analysis. This result allowed us to assign a (2*R*, 2'*S*) stereochemistry to compound (**4c**) and (2*S*, 2'*S*) to compound (**4d**) (Scheme 4).



Scheme 4

In conclusion, the tetrasubstituted double bond of piperidine β-enamino ester (**1**) was diastereoselectively reduced to give (2*S*, 2'*R*)-piperidinepropanoate. This compound was found to be diastereomeric to that obtained according to a two-step reduction/alkylation sequence from piperidine trisubstitued β-enamino ester (**2**). Considering that compound (**1**) had been in fact obtained by alkylation of **2**, these results constitute a diastereodivergent synthesis of 2-piperidin-2-ylpropanoates.

EXPERIMENTAL

General. The general experimental procedures were carried out as previously described.[2]

Methyl (2*R*)-2-{(2*R*)-1-[(1*S*)-1-phenylethyl]piperidin-2-yl}propanoate (4a). To a stirred cooled (–78°C) solution of LDA (4.77 mmol) in THF (20 mL) was added dropwise a solution of **3a**[8] (1.08g, 4.15 mmol) in THF. The reaction mixture was stirred at 0°C for 3 hours, then MeI (2.6 mL, 20.75 mmol) was added. After stirring overnight at rt, a saturated aqueous NH_4Cl solution (10 mL) was added. The aqueous layer was extracted with AcOEt (3×10 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under vacuo. The crude product was filtered over silica gel pad eluting with AcOEt/cyclohexane 1:1 and then transformed into the picrate which was crystallized in ethanol to give pure picric salt of **4a** (mp 155°C; $[\alpha]^{20}_D$ – 7 (*c* 0.94, CH_2Cl_2)). Compound (**4a**) was

liberated with K_2CO_3 and extracted from the cake with CH_2Cl_2 to be finally obtained as a solid in 73% yield. mp 39°C; $[\alpha]^{20}_D$ – 20.5 (*c* 1.1, CH_2Cl_2); IR (neat) 2945, 1715 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.14 (d, *J* = 7 Hz, 3H), 1.31 (d, *J* = 6.75 Hz, 3H), 1.22–1.68 (m, 6H), 2.31–2.40 (m, 1H), 2.57–2.66 (m, 1H), 2.84–2.91 (m, 1H), 3.05–3.16 (m, 1H), 3.69 (s, 3H), 4.13 (q, *J* = 6.75 Hz, 1H), 7.20–7.42 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 10.9, 12.4, 23.4, 24.5, 24.7, 40.3, 44.3, 51.7, 55.1, 58.8, 126.5, 127.6, 128.0, 144.8, 176.0; Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.17; H, 9.15; N, 5.09. Found: C, 73.89; H, 9.22; N, 5.12.

Crystal data of the picrate of **4a**: $C_{23}H_{28}N_4O_9$ (504.50) orthorhombic, space group $P2_12_12_1$; *a* = 7.6014(8), *b* = 17.141(3), *c* = 19.230(3) Å, *V* = 2505.6(6) $Å^3$; *Z* = 4; D = 1.34 g cm^{-3}; μ(Mo-Kα) = 1.04 cm^{-1}, 16107 reflections collected, 2212 observed ($I > 1.65\sigma(I)$); R = 0.0483; R_w = 0.0510; goodness of fit = 1.0722 .

***tert*-Butyl (2*R*)-2-[(1*R*)-2-methoxy-1-methyl-2-oxoethyl]piperidine-1-carboxylate (5a).** A solution of compound **(4a)** (333 mg, 1.21 mmol) in AcOMe (40 mL) was subjected to hydrogenation (1 atm) in the presence of $Pd(OH)_2/C$ (0.2 equiv in weight) and Boc_2O (552 mg, 2.53 mmol) at rt. The progress of the reaction was monitored by GC. The reaction mixture was filtered, the residue thoroughly washed with MeOH and the combined filtrates were concentrated in vacuo. Silica gel column chromatography (AcOEt/cyclohexane: 15:85) afforded pure compound **(5a)** (315 mg, 96%). $[\alpha]^{31}_D$ + 13.5 (*c* 1.1, $CHCl_3$); IR (neat) 1685, 1730 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.13 (d, *J* = 7 Hz, 3H), 1.43 (s, 9H), 1.49–1.61 (m, 4H), 1.73–1.79 (m, 2H), 2.88–3.05 (m, 2H), 3.63 (s, 3H), 3.95-4.05 (m, 1H), 4.25-4.35 (m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.6, 18.8, 25.2, 25.5, 28.3, 38.5, 39.3, 51.5, 53.5, 79.2, 154.4, 175.1; HRMS (ESI^+) m/z 294.1676 ($M+Na^+$, $C_{14}H_{25}NO_4Na^+$ requires 294.1676).

***tert*-Butyl (2*R*)-2-[(1*S*)-2-methoxy-1-methyl-2-oxoethyl]piperidine-1-carboxylate (5b).** A solution of compound **(1)**[12] (376 mg, 1.38 mmol) in MeOH (16 mL) was subjected to hydrogenation (1 atm) in the presence of 10% Pd/C (30 mg, 0.08 equiv in weight) at rt for 12h. Then, Pd/C (30 mg) was added and the reaction was continued for 12h more. The reaction mixture was filtered off, the residue thoroughly washed with MeOH and the combined filtrates were concentrated under vacuo. To the crude residue dissolved in CH_2Cl_2 (40 mL) were added Boc_2O (660 mg, 3 mmol) and NEt_3 (2 mL, 14.3 mmol). The reaction was stirred overnight at rt. CH_2Cl_2 was then added and the resulting mixture was successively washed with a 1M HCl solution, a saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and concentrated in vacuo. Column chromatography on silica gel (AcOEt/cyclohexane: 5:95) afforded a 94:6 mixture (**5b**) and *ent*-(**5b**) (202 mg, 54 %) as a colorless oil, along with a 6:4 mixture of **5a** and (**5b**)-*ent*-(**5b**) (30 mg, 8 %). For a 94:6 mixture of (**5b**)-*ent*-(**5b**): $[\alpha]^{20}_D$ – 5.5 (*c* 1.27, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.09 (d, *J* = 7 Hz, 3H), 1.47 (s, 9H), 1.40–1.72 (m, 7H), 2.50–2.77 (m, 1H), 2.92–3.04 (m, 1H), 3.69 (s, 3H), 3.80–4.20 (m, 1H), 4.30–4.60 (m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$)

δ 14.5, 19.2, 25.3, 27.5, 28.4, 38.4, 39.3, 51.7, 53.0, 79.6, 155.2, 175.8; Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 62.25; H, 9.56; N, 5.08.

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15. Determined by GC analysis.
16. In ref. 11, the experimental details were not described and the obtained alkylated piperidine β-amino esters were only partially characterized. Moreover, the optical rotation values have been mistakenly reported as positive, and must be read as negative.
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18. A similar result was obtained for pyrrolidine homologue alkylation: see ref. 9.
19. The procedure was improved by the successful purification of **1** by a very short column filtration on silica gel (AcOEt) with a similar yield (87%).
20. A similar mixture of four diastereomers was obtained when using PtO_2 as the catalyst.
21. We have not succeeded in avoiding the debenzylation of **1** by lowering the amount of catalyst used, as already reported for pyrrolidine analogues.[10]
22. The reaction was also conducted starting from enantiopure piperidine (**4a**) to afford pure compound (**5a**).
23. $Pd(OH)_2/C$ catalyzed hydrogenation (0.15 equiv in weight) of **1** was also carried out with a similar diastereoselectivity, provided that two additions of the catalyst were performed successively (0.05 equiv for 12h and 0.10 equiv for 3h).