Asymmetric Reduction of β-Ketoesters and Chiral β-Iminoesters: Impact of a α-Quaternary Stereocenter

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ABSTRACT Diastereomeric reduction of nonactivated, hindered β-keto and chiral β-iminoesters are described. The influence of a α-stereocontrolled center on the efficiency and stereoselectivity of the reduction was studied. Reaction conditions were optimized to synthesize β-hydroxy- and β-aminoesters in good yields. In the case of chiral β-iminoesters, influence of matched/mismatched diastereomeric pairs has been assessed. *Chirality 23:265–271, 2011.*

KEY WORDS: asymmetric synthesis; diastereoselectivity; β-aminoesters; β-hydroxyesters

INTRODUCTION

Chiral β-hydroxy, β-aminoesters, and acids are synthetically valuable building blocks for the construction of natural products and pharmaceuticals.[1–3] An access to such compounds can be envisioned by an atom economic method, such as the stereoselective reduction of β-keto and β-iminoesters, respectively: this strategy proved to be efficient in the synthesis of RWJ-53308, a GP IIb/IIIa antagonist.[4] Although widely studied, this strategy appears restricted to nonhindered or activated derivatives. Indeed, only few examples describe the asymmetric reduction of sterically hindered derivatives possessing a quaternary carbon atom on the α-position. In these cases, reduction is usually performed by asymmetric catalytic hydrogenation using ruthenium and rhodium chiral complexes[5–13] or chiral reducing agents, such as diisopinocamphenylchloroborane.[14] In addition, the reduction of β-ketoesters, bearing a pre-existing α-quaternary chiral center is scarcely reported[15–18] and, to the best of our knowledge, only one example showed the reduction of chiral β-iminoesters by hydride transfer.[19] Due to the wide occurrence of these chiral β-hydroxyester and β-aminoester fragments in more complex synthetic or natural targets, there is still a steady demand for the development of practical methodology exempt from external chiral reductant.

In this preliminary study, we report the diastereoselective reduction of nonactivated hindered β-keto and chiral β-iminoesters, bearing a α-quaternary stereocontrolled center, by boro- and lithio-hydride derivatives.

EXPERIMENTAL

Commercial reagents were used without purification. β-Iminoester **1a-b** and β-ketoester **2a-c** were synthesized according classical procedures. [20–22] Prior to use, THF was freshly distilled from sodium-benzophenone and toluene from CaH_2. All anhydrous reactions were carried out under argon atmosphere. Analytical thin layer chromatography was performed on Merck 60F-254 precoated silica (0.2 mm) on glass and was revealed by UV-light or Kägi-Misher reagent. All flash chromatography separations were performed with Merck Kieselgel (40–63 μm). Melting points were recorded on an Electrothermal digital apparatus and were uncorrected. Infrared (IR) spectra were obtained as neat films and were recorded on Bruker Vector 22 spectrophotometer. ^1H and ^{13}C spectra were recorded, respectively, at 300 and 75 MHz on a Bruker Avance 300. $CDCl_3$ was used as internal reference. Specific rotations $[\alpha]_D^{20}$ were measured on a PolAAr32 polarimeter with sodium (589 nm) lamp at 20°C in a 1 dm-cell. Diastereomeric excesses (de) were evaluated by ^1H NMR spectroscopy. Positive EI-MS and APCI-MS spectra were recorded respectively on a Bruker Esquire LC.

(2S)-5-Benzyl 1-ethyl 2-methyl-2-(1-((1R)-1-phenylethylimino)ethyl)pentanedioate 1′b.

To a solution of (*R*)-1-phenylethylamine (1.2 equiv) and freshly distilled triethylamine (6 equiv) in anhydrous CH_2Cl_2 (C = 0.1 *M*), was added dropwise, at 0°C and under inert atmosphere, $TiCl_4$ (0.5 equiv) then compound **1b** (1 equiv). After stirring the mixture at reflux for 24 h, Et_2O was added. The reactive medium was filtered over celite and the filtrate was concentrated to give, without purification, the desired product **1′b** as yellow oil. RMN ^1H: 7.40–7.05 (10 Harom, m), 5.15 + 5.13 (CH_2, s), 4.19 + 4.16 (CH_2, q, *J*= 7.2), 2.95 (CH, m), 2.20 (CH_2, m), 2.15 (CH_3, s). 1.80 (CH_2, m), 1.27 + 1.28 (CH_3, t, *J* = 7.2), 1.15 (CH_3, d, *J* = 6.4), 1.00 (CH_3, s); RMN ^{13}C: 176.4 + 176.2 + 173.1 + 172.9 (COO), 160.1 (C=N), 145.7 + 143.8 (C_q), 126.6–128.4 (CH), 72.0 + 72.2 (CH_2), 60.3 + 60.2 (CH_2), 52.3 (CH), 50.7 + 50.1 (C_q), 31.2 + 30.6 (CH_2), 28.1 (CH_2), 25.75 (CH_3), 22.4 + 22.8 (CH_3), 18.2 (CH_3), 15.4 + 15.3 (CH_3); IR (cm^{-1}): 3000, 1750, 1680, 1460, 1300.

Method A: Reduction with $NaBH_4$. To a solution of β-ketoester **2a**/β-iminoester **1a** (1 equiv) in anhydrous THF (C = 1 M), was added MeOH (1 equiv) and $NaBH_4$ (1 equiv), at −78°C and under inert atmosphere. After stirring the mixture at −78°C during 9 h, water was added, THF was evaporated and the aqueous layer was extracted three times with CH_2Cl_2. The resulting organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (cyclohexane/AcOEt: 7/3) to yield the desired hydroxyester **3a** and lacton **4**/aminoester **5a**.

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Method B: Luche reduction. To a solution of β-ketoester **2a-b** (1 equiv) in anhydrous MeOH (C = 1 M) was added $CeCl_3.7H_2O$ (1.3 equiv) at room temperature. After stirring the mixture for 1 h at room temperature, a suspension of $NaBH_4$ (1 equiv) in anhydrous MeOH (C = 2 M) was added dropwise, at −78°C and under inert atmosphere. After stirring the mixture at −78°C during 3 h, water was added, MeOH was evaporated and the aqueous layer was extracted three times with CH_2Cl_2. The resulting organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (cyclohexane/AcOEt: 7/3) to yield the desired hydroxyester **3a-b** and lacton **4**.

Method C: Reduction with $NaHB(O_2CiPr)_3$. $NaBH_4$ (3 equiv) was slowly added to isobutyric acid (20 equiv) at 0°C and under inert atmosphere. After stirring the mixture for 30 min at room temperature, anhydrous toluene was added and the resulting solution of $NaHB(O_2CiPr)_3$ in toluene (C = 1 M) was cooled to 0°C. A solution of β-ketoester **2a-c**/β-iminoester **1a-b** or **1′b** (1 equiv) in anhydrous toluene (C = 0.2 M) was then added at 0°C. After stirring the mixture for 5 h at 0°C, with regular addition of $NaBH_4$ (1 equiv every hour), water was added, then a solution of NaOH 3 M until pH>10. The reactive medium was extracted three times with AcOEt. The resulting organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (cyclohexane/AcOEt: 7/3) to yield the desired hydroxyester **3a-c** and lacton **4**/ β-aminoester **5a-b**.

Method D: Reduction with $Zn(BH_4)_2$. To a solution of β-ketoester **2a**/β-iminoester **1a-b** or **1′b** (1 equiv) in anhydrous THF (C = 0.4 M) was added, at 0 °C and under inert atmosphere, a freshly prepared solution of $Zn(BH_4)_2$ in THF (3 equiv). After stirring the mixture for 1 h at 0°C then for 2 h at room temperature, water was added, THF was evaporated and the aqueous layer was extracted three times with Et_2O. The resulting organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (cyclohexane/AcOEt: 7/3) to yield the desired hydroxyester **3a** and lacton **4**/β-aminoester **5a-b**.

Method E: Reduction with L-Selectride. To a solution of β-ketoester **2a**/β-iminoester **1b-1′b** (1 equiv) in anhydrous THF (C = 0.5 M) was added, at −78°C and under inert atmosphere, L-Selectride (5 equiv). After stirring the mixture for 5 h at room temperature, a saturated solution of NH_4Cl was added, THF was evaporated and the aqueous layer was extracted three times with CH_2Cl_2. The resulting organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (cyclohexane/AcOEt: 7/3) to yield the desired hydroxyester **3a** and lacton **4**/ β-aminoester **5b**.

Method F: Reduction with $LiAlH(OtBu)_3$. To a solution of β-ketoester **2a**/β-iminoester **1b-1′b** (1 equiv) in anhydrous THF (C = 0.5 M) was added, at −78°C and under inert atmosphere, $LiAlH(OtBu)_3$ (1.2 equiv). After stirring the mixture for 3 h at −78°C then 3h at 0°C, NaOH 2 M was added, THF was evaporated and the aqueous layer was extracted three times with CH_2Cl_2. The resulting organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (cyclohexane/AcOEt: 7/3) to yield the desired compound hydroxyester **3a** and lacton **4**/ β-aminoester **5b**.

Method G: Reduction with $NaBH_4/ZnCl_2$. To a solution of β-iminoester **1b** (1 equiv) in anhydrous THF (C = 1 M) was added, at 0°C and under inert atmosphere, a solution of $ZnCl_2$ (3 equiv) in anhydrous THF (C = 10 M). After stirring the mixture for 1 h at 0°C, $NaBH_4$ (6 equiv) was added. After stirring the mixture for 1 h at 0°C than for 2 h at room temperature, a saturated solution of NH_4Cl was added, THF was evaporated and the aqueous layer was extracted three times with Et_2O. The resulting organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (cyclohexane/AcOEt: 7/3) to yield the desired β-aminoester **5b**.

(+) (2S)-5-Tert-Butyl 1-ethyl 2-((1R)-1-hydroxyethyl)-2-methylpentanedioate 3a

Rf = 0.13 cyclohexane/ACOEt: 7/3; ^{1}H NMR: 4.19+4.16 (CH_2, q, J = 7.2), 3.90 (CH, m), 2.73 (bs, OH), 2.20 (CH_2, m), 1.79 (CH_2, m), 1.40+1.30 ($C(CH_3)_3$, s), 1.27+1.28 (CH_3, t, J = 7.2), 1.05 (CH_3, d, J = 6.4), 1.01 (CH_3, s); ^{13}C NMR: 176.4+176.2+173.1+172.9 (COO), 80.3+80.2 (C_q), 71.4+71.3 (CH), 60.3+60.2 (CH_2), 50.7+50.1 (C_q), 31.2+30.6 (CH_2), 28.1 (CH_2), 24.7+23.4 (CH_3), 15.4+15.3 (CH_3), 16.8+16.6 (CH_3), 24.7+23.4 (CH_3); $[\alpha]_D^{20}$= +6 (c 1.0 in DCM, de 31%) IR (cm^{-1}): 3510, 1750, 1460, 1300. ESI-MS: *m/z* = 571 ($[2M+Na]^+$, 100%), 513 (26%), 497 (42%), 378 (38%), 297 ($[M+Na]^+$, 69%).

(−) (2S)-5-Benzyl 1-ethyl 2-((1R)-1-hydroxyethyl)-2-methylpentanedioate 3b

Rf = 0.15 (cyclohexane/AcOEt: 8.5/1.5); ^{1}H NMR: 7.40–7.05 (5 Harom, m), 5.15+5.13 (CH_2, s), 4.19+4.16 (CH_2, q, J = 7.2), 3.90 (CH, m), 2.73 (bs, OH), 2.20 (CH_2, m), 1.80 (CH_2, m), 1.27+1.28 (CH_3, t, J = 7.2), 1.15 (CH_3, d, J = 6,4), 1.05 (CH_3, s); ^{13}C NMR 176,4+176.2+173.1+172.9 (COO), 145.7+143.8 (C_q), 126.6–128.4 (CH), 72.0+72.2 (CH_2), 71.4+71.3 (CH), 60.3+60.2 (CH_2), 50.7+50.1 (C_q), 31.2+30.6 (CH_2), 28.1 (CH_2), 22.4+22.8 (CH_3), 16.8+16.6 (CH_3), 15.4+15.3 (CH_3); $[\alpha]_D^{20}$= −5 (c 1.1 in DCM, de 67%); IR (cm^{-1}): 3410, 1750, 1714, 1460, 1300. ESI-MS: *m/z* = 639 ($[2M+Na]^+$, 30%), 531 (34%), 331 ($[M+Na]^+$, 100%), 223 (42%).

(2S)-1-Ethyl 5-methyl 2-((1R)-1-hydroxyethyl)-2-methylpentanedioate 3c

^{1}H NMR: 4.19+4.16 (CH_2, q, J = 7.2), 3.90 (CH, m), 3.62+3.64 (CH_3, s), 2.71 (bs, OH), 2.20 (CH_2, m), 1.80 (CH_2, m), 1.27+1.28 (CH_3, t, J = 7.2), 1.06 (CH_3, d, J = 6,4), 1.00 (CH_3, s); ^{13}C NMR: 176,4+176.2+173.1+172.9 (COO), 72.0+72.1 (CH), 60.3+60.2 (CH_2), 51.0 (CH_3), 50.7+50.1 (C_q), 31.2+30.6 (CH_2), 29.2 (CH_3), 28.1 (CH_2), 22.4+22.8 (CH_3), 15.4+15.3 (CH_3); IR (cm^{-1}): 3510, 1750, 1460, 1300. (An inseparable mixture of hydroxyester **3c** and lacton **4** was systematically obtained.)

(+) (2R,3S)-Ethyl 2,3-dimethyl-6-oxo-tetrahydro-2H-pyran-3-carboxylate 4

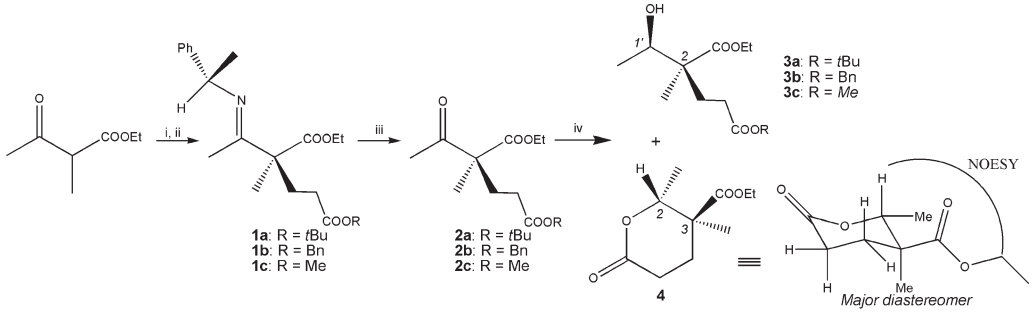
^{1}H NMR: 4.19 (CH_2, q, J = 7.2), 4.78 (CH, m), 2.67+2.53 (CH_2, m), 2.35+1.78 (CH_2, m), 1.40+1.30 ($C(CH_3)_3$, s), 1.32 (CH_3, d, J = 6.4), 1.27 (CH_3, t, J = 7.2), 1.21 (CH_3, s); ^{13}C NMR: 174.5+170.9 (COO), 78.8 (CH), 61.4 (CH_2), 44.3 (C_q), 29.8 (CH_2), 26.7 (CH_2), 16.5 (CH_3), 16.3 (CH_3), 14.1 (CH_3); $[\alpha]_D^{20}$ = +15 (c 0.8 in DCM, de 100%). IR (cm^{-1}): 1746, 1460, 1300. ESI-MS: *m/z* = 423 ($[2M+Na]^+$, 100%), 320 (21%), 223 $[M+Na]^+$, 44%).

(−) (2S)-5-tert-Butyl 1-ethyl 2-methyl-2-((1S)-1-((1S)-1-phenylethylamino)-ethyl)pentanedioate 5a

Rf = 0.43 (cyclohexane/ AcOEt: 8/2); ^{1}H NMR: 7.93–7.90 (5 Harom, m), 4.19+4.16 (CH_2, q, J = 7.2), 3.74 (CH, m), 2.95 (CH, m), 3.18–3.00 (CH_2, m), 2.73 (NH, bs), 2.27–2.05 (CH_2, m), 1.32 (CH_3, s), 1.25+1.23 (CH_3, t, J= 7.2, H_1), 1.15 (CH_3, d, J = 6.4), 1.05 (CH_3, d, J = 6,4); ^{13}C NMR: 171,5+171.4+170.8+170.6 (COO), 145.7+143.8 (C), 126.6–128.4 (CH), 82.1+82.4 (C_q), 61.7+61.5 (CH_2), 56.5+56.2 (CH), 52.3(CH), 52.0 (C_q), 30.8+30.2 (CH_2), 28.1 (CH_3), 27.5 (CH_2), 22.8+22.4 (CH_3), 18.5 (CH_3), 16.8+16.6 (CH_3), 15.4+15.3 (CH_3); $[\alpha]_D^{20}$= −12 (*c* 0.25 in DCM, de 38%); IR (cm^{-1}): 3000, 1750, 1460, 1300. APCI-MS: *m/z* = 402 (32%), 378 ($[M+H]^+$, 100%).

(−) (2S)-5-Benzyl 1-ethyl 2-methyl-2-((1S)-1-((1S)-1-phenylethylamino)ethyl) pentanedioate 5b

Rf = 0.5 (cyclohexane/AcOEt: 85:15); ^{1}H NMR: 7.40–7.05 (10 Harom, m), 5.15+5.13 (CH_2, s), 4.19+4.16 (CH_2, q, J = 7.2), 3.70 (CH, m), 2.95 (CH, m), 2.73 (NH, bs), 2.20 (CH_2, m), 1.80 (CH_2, m), 1.27+1.28 (CH_3, t, J = 7.2), 1.15 (CH_3, d, J = 6.4), 1.05 (CH_3, d, J = 6,4) , 1.00 (CH_3, s); ^{13}C NMR: 176.4+176.2+173.1+172.9 (COO), 145.7+143.8 (C_q), 126.6–128.4 (CH), 72.00+72.2 (CH), 60.3+60.2 (CH_2), 56.5+56.2 (CH_2), 52.3 (CH), 50.7+50.1 (C_q), 31.2+30.6 (CH_2), 28.1 (CH_2), 22.4+22.8 (CH_3),



(i) (*S*)-1-phenylethylamine, APTS, toluene, Dean Stark, reflux, overnight; (ii) CH_2=CH-COOR, hydroquinone (cat.), THF, reflux, 5 to 8 days; (iii) AcOH 10%, THF, r.t, 2 h; (iv) Conditions summarized in table 1

Scheme 1. Synthesis of the iminoesters **1a-1c**, ketoesters **2a-2c**, and hydroxyesters **3a-3c**.

18.2 (CH_3), 16.8+16.6 (CH_3), 15.4+15.3 (CH_3); $[\alpha]_D^{20} = -15$ (c 0.2 in DCM, de 38%). IR (cm^{-1}): 3000, 1750, 1460, 1300. APCI-MS: *m/z* = 412 ($[M+H]^+$, 100%).

(−) (2S)-5-Benzyl 1-ethyl 2-methyl-2-((1S)-1-((1R)-1-phenylethylamino)ethyl) pentanedioate 5′b

Rf = 0.5 (cyclohexane/AcOEt: 85:15); ^{1}H NMR: 7.40–7.05 (10 Harom, m), 5.15+5.13 (CH_2, s), 4.19+4.16 (CH_2, q, J = 7.2), 3.70 (CH, m), 2.95 (CH, m), 2.75 (NH, bs), 2.20 (CH_2, m), 1.80 (CH_2, m), 1.27+1.28 (CH_3, t, J = 7.2), 1.15 (CH_3, d, J = 6.4), 1.05 (CH_3, d, J = 6,4) , 1.00 (CH_3, s); ^{13}C NMR: 176,4+176.2+173.1+172.9 (COO), 145.7+143.8 (C_q), 126.6–128.4 (CH), 72.00+72.2 (CH), 60.3+60.2 (CH_2), 56.5+56.2 (CH_2), 52,3 (CH), 50.7+50.1 (C_q), 31.2+30.6 (CH_2), 28.1 (CH_2), 22.4+22.8 (CH_3), 18.2 (CH_3), 16.8+16.6 (CH_3), 15.4+15.3 (CH_3); $[\alpha]_D^{20} = -4.5$ (c 0.2 in DCM, de 45%). IR (cm^{-1}): 3000, 1750, 1460, 1300. APCI-MS: *m/z* = 412 ($[M+H]^+$, 100%).

(−) (2S,3S)-Ethyl 2,3-dimethyl-6-oxopiperidine-3-carboxylate 6

A solution of β-aminoester **5a-b** (1 equiv) and catalytic amount of Pd/C in anhydrous MeOH (C = 0.1 M) was stirred at room temperature for 2 h under an hydrogen atmosphere. The reactive medium was then filtered over celite and the filtrate was concentrated to yield the desired lactam **6** as yellow oil (69% yield). Rf = 0.5 (cyclohexane/AcOEt: 8.5/1.5); ^{1}H NMR: 7.07 (NH), 4.11 (CH_2, q, J =7.2), 3.39 (CH, m), 2.43 (CH_2,dd, J_1 =7, J_2=19), 2.14 (CH_2, dd, J_1 = 8, J_2 = 15), 1.26 (CH_3, s), 1.21 (CH_3, t, J =7.2), 1.16 (CH_3, d, J =6.4); ^{13}C NMR: 174.1+171.5 (COO), 60.7 (CH_2), 54.8 (CH), 43.5 (C_q), 28.0 (CH_2), 27.3 (CH_2), 22.0 (CH_3), 17.4 (CH_3), 14.0 (CH_3); $[\alpha]_D^{20} = -14$ (c 3.0 in DCM, de 67%). IR (cm^{-1}): 1750, 1672, 1460, 1300. APCI-MS: *m/z* = 399 ($[2M+H]^+$, 95%), 200 ($[2M+H]^+$, 100%).

RESULTS AND DISCUSSION

The (*S*)-β-iminoesters **1a-c** and the (*S*)-β-ketoesters **2a-c** have been synthesized by asymmetric Michael reaction according the literature procedure (Scheme 1). Good yields (40–85%) and excellent enantiomeric excesses (85–95%) were obtained.[20–22]

We first carried out the reduction of β-ketoesters **2a-c** using a variety of reducing agents (Scheme 1, Table 1). Sodium borohydride was used alone or in Luche reaction condition.[23] Sodium tris(isobutyroxy)borohydride,[24,25] zinc borohydride,[26,27] L-Selectride,[28,29] and lithium tri-*tert*-butoxyaluminium hydride[30,31] have also been assessed. The reaction was monitored by TLC and diastereomeric excesses (de) were measured by ^{1}H NMR experiments. All reduction reactions were first attempted at −78°C. If no reaction occurred at this low temperature, the reaction mixture was gradually warmed to −10°C, then to 0°C and in final to ambient temperature until complete starting ketone consumption. The optimized reaction conditions have been summarized in Table 1.

The desired β-hydroxyesters **3a-c** were purified by flash chromatography on silica gel. However, in the case of the hydroxyesters **3b** and **3c**, partial annulation occurred during purification leading the lactone **4** (Scheme 1). Lactonisation proceeded predominantly in the case of the methyl hydroxyester **3c**. The steric hindrance of the *tert*- butyl ester group of **3a** circumvented the side reaction of lactonisation. Moreover, both the reduction product and the lactonisation byproduct present the same diastereomeric excess, excluding a kinetic control of the cyclisation whatever the diastereomeric alcohol.

TABLE 1. Diastereoselective reduction of β-ketoesters 2a-c

Entry	Starting material	Method	Reductive agent and reaction conditions	Yields (%)[a] 3a-c	Yields (%)[a] 4	De (%)[b]
1	**2a**	A	$NaBH_4$ 1 equiv, MeOH 1 equiv THF, −78°C, 9 h	65	–	7
2	**2a**	B	$NaBH_4$ 1 equiv/$CeCl_3$ 1.3 equiv MeOH, −78°C, 3 h	43	–	11
3	**2a**	C	$NaHB(O_2CiPr)_3$ 3 equiv toluene, 0°C, 7 h	84	–	31
4	**2a**	D	$Zn(BH_4)_2$ 3 equiv THF 0°C, 1 h then 24°C, 3 h	44	24	20
5	**2a**	E	L-Selectride 5 equiv THF 24°C, 5 h	72	–	17
6	**2a**	F	$LiAlH(OtBu)_3$ 1.2 equiv THF −78°C 3 h then 0°C, 3 h	79		15
7	**2b**	B	$NaBH_4$ 1 equiv/$CeCl_3$ 1.3 equiv MeOH, −78°C, 3 h	41	–	10
8	**2b**	C	$NaHB(O_2CiPr)_3$ 3 equiv toluene, 0°C, 7 h	79	6	23
9	**2c**	C	$NaHB(O_2CiPr)_3$ 3 equiv toluene, 0°C, 7 h	20	62	11

[a]Isolated yields after column chromatography.
[b]Determined by ^{1}H NMR.

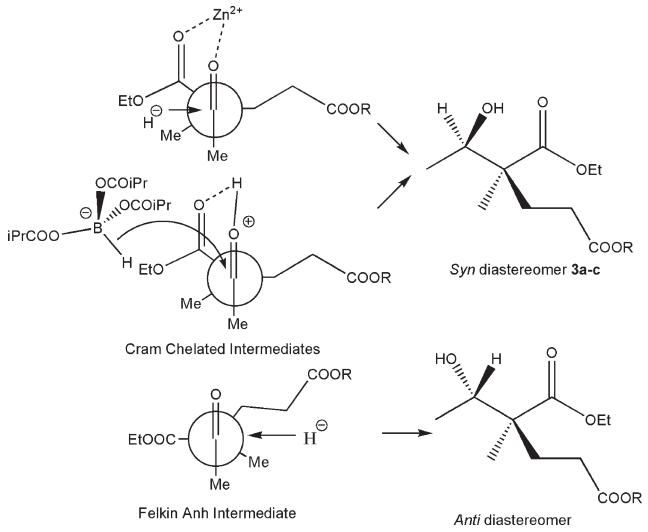


Fig. 1. Chelated versus nonchelated intermediates for ketoesters **2a-c**.

Use of sodium borohydride gave the desired hydroxyester **3a** in good chemical yield but without notable stereoselectivity (Entry 1), suggesting the poor influence of the stereocontrolled quaternary center on the diastereoselectivity in those conditions. Addition of a chelating agent, such as cerium chloride did not improve diastereoselectivity or chemical yield (Entry 2). Likewise, hindered reductive agents, such as L-selectride and lithium tri-*tert*-butoxyaluminium hydride did not allow an enhancement of diastereoselectivity (Entries 5 and 6). From this study, better diastereoselectivities were obtained using zinc borohydride or $NaHB(O_2CiPr)_3$ (Entries 3, 4, 8, and 9). In this last case, the hindered isobutyrate hydride has a slight impact on diastereoselectivity, de rising up to 31%. On the other hand, the reduction by $ZnBH_4$ resulted in an increasing amount of the nondesired lactone (Entry 4).

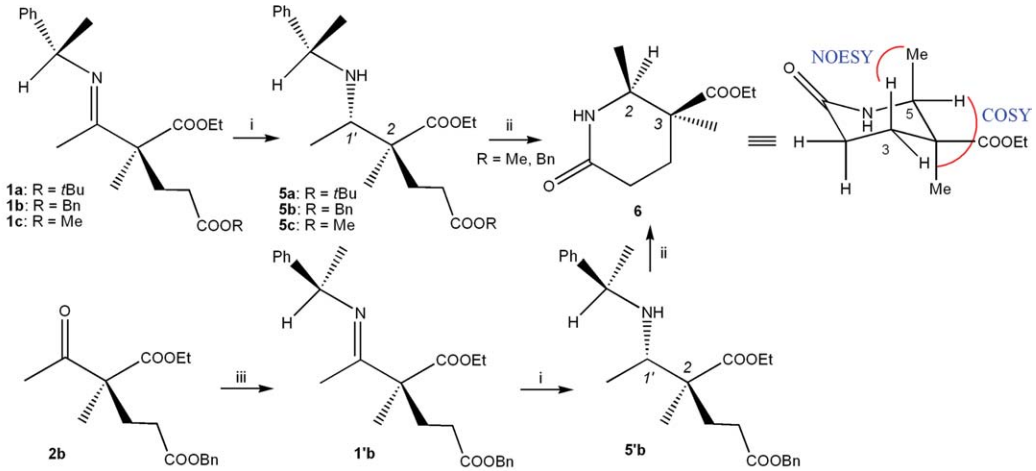
Applied to a diastereomerically pure major lacton **4**, one and two dimensional ^1H NMR experiments showed a spatial correlation between the hydrogen of the tertiary chiral center and the ester moiety (Scheme 1). These NMR spectroscopy analyses ascertained the relative configuration of the vicinal chiral centers in the major lacton diastereomer **4**. Moreover, whatever the reaction conditions and the reductive agents used, the same major diastereomer **4** was observed. As a result, absolute configuration of the major hydroxyesters **3a-c** were shown to be a (*2S, 1′R*) configuration. The stereochemical outcome of the reduction of ketoester could find an explanation on the basis of both a cyclic Cram chelated with Zn(II) or borate intermediate and a nonchelated Felkin-Anh one (Fig. 1).[31]

The Cram chelated model led to the major syn diastereomer, the Felkin Anh nonchelated one to the minor anti diastereomer. Chelated intermediate was slightly preferred to nonchelated intermediate, giving a mixture of the syn and anti hydroxyesters. This lack of facial diastereoselectivity might be due to the quaternary carbon atom in the α-position which allowed insufficient side differentiation and/or made such complexation more difficult. Our results confirmed the previous work of Alvarez-Ibarra et al.,[16] which concluded that the diastereoselectivity was highly dependant of ketoester's structure, reducing agent, solvent and additive.

Due to the inadequacy of asymmetric induction by the α-quaternary carbon atom, we studied the influence of an additionnal chiral center borne by an imino group instead of the carbonyl moiety.

The same reducing agents were evaluated on the chiral β-iminoesters **1a-b** (Scheme 2, Table 2). Similarly, the reduction of the iminoester **1a** by sodium borohydride gave the corresponding amino compound with very poor diastereoselectivity (Entry 1). $Zn(BH_4)_2$ (Entries 3 and 5), $NaHB(O_2CiPr)_3$ (Entries 2 and 4), L-selectride (Entry 7) and lithium tri-*tert*-butoxyaluminium hydride (Entry 8) reduced iminoesters **1a-c** less efficiently than ketoesters **2a-c** in terms of chemical yields. However, the presence of the chiral imine part caused a global improvement of diastereoselectivity, comparatively to the corresponding ketoesters. We can also note that a $ZnCl_2/NaBH_4$ mixture[33,34] instead of freshly prepared $Zn(BH_4)_2$ did not modified neither diastereoselectivity nor chemical yield (Entries 5 and 6).

To evaluate the matched/mismatched diastereomeric pairs effect on the asymmetric induction, the diastereomeric iminoester **1′b** was prepared in 67% yield according to a method dedicated to hindered imines synthesis (Scheme 2).[35] Never-



Scheme 2. Reduction of iminoesters **1a-1b** and **1′b** and access to the lactam derivative 6. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

TABLE 2. Diastereoselective reduction of β-iminoesters 1a-b and 1′b

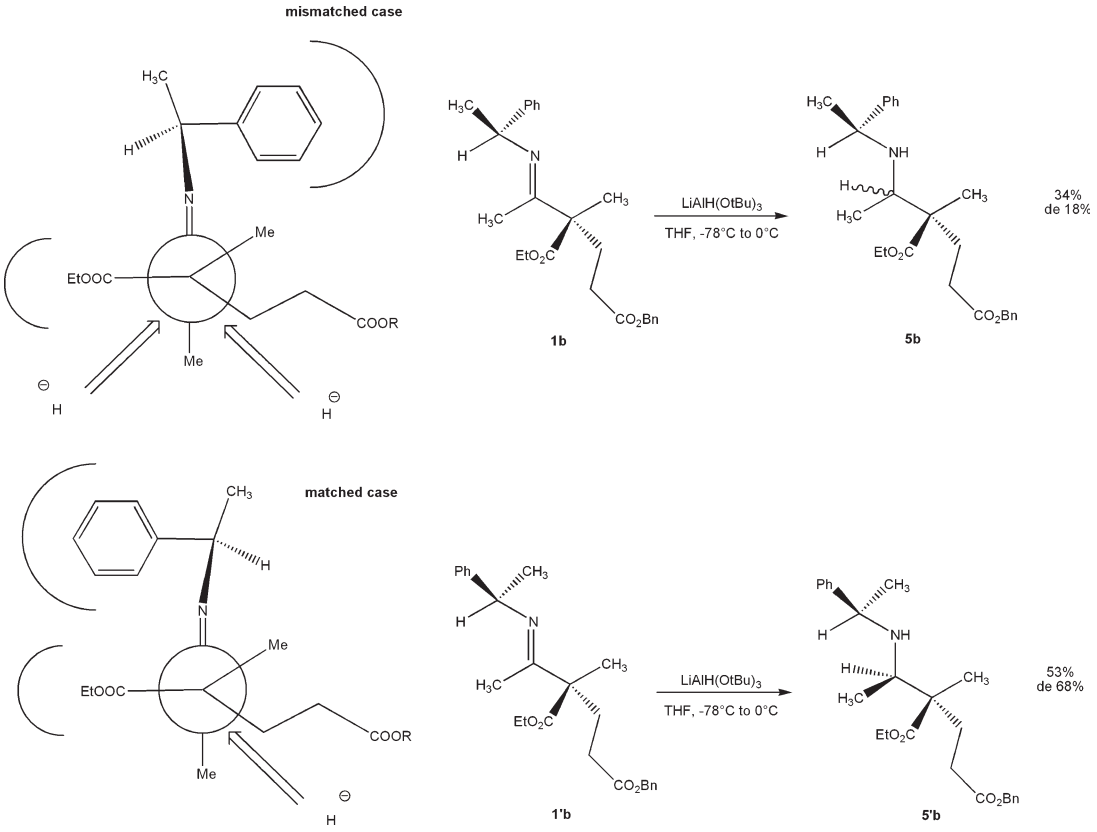
Entry	Starting material	Method	Reductive agent and reaction conditions	Yield (%)[a]	De (%)[b]
1	**1a**	A	$NaBH_4$ 1 equiv, MeOH 1 equiv THF, −78°C, 9 h	75	10
2	**1a**	C	$NaHB(O_2CiPr)_3$ 3 equiv THF toluene, 0°C, 7 h	82	50
3	**1a**	D	$Zn(BH_4)_2$ 3 equiv THF 0°C 1 h then 24°C 2 h	56	45
4	**1b**	C	$NaHB(O_2CiPr)_3$ 3 equiv Toluene, 0°C, 5 h	23	45
5	**1b**	D	$Zn(BH_4)_2$ 3 equiv THF 0°C 1 h then 24°C 2 h	49	32
6	**1b**	G	$NaBH_4$ 6 equiv/ $ZnCl_2$ 3 equiv THF, 0°C 1 h then 24°C 2 h	55	31
7	**1b**	E	L-Selectride 5 equiv THF 24°C, 5 h	43	27
8	**1b**	F	$LiAlH(OtBu)_3$ 1.2 equiv THF −78°C 3 h then 0°C, 3 h	34	18
9	**1′b**	C	$NaHB(O_2CiPr)_3$ 3 equiv Toluene, 0°C, 4 h	47	45
10	**1′b**	D	$Zn(BH_4)_2$ 3 equiv THF 0°C 1 h then 24°C 2:30 h	45	17
11	**1′b**	E	L-Selectride[c] 5 equiv THF 24°C, 5 h	46	67
12	**1′b**	F	$LiAlH(OtBu)_3$ 1.2 equiv THF −78°C 3 h then 0°C, 3 h	53	68

[a]Isolated yields after column chromatography.
[b]Determined by ^1H NMR.
[c]5 equiv were required to total starting material consumption.

theless, attempts to synthesize the bulky *tert*-butylester analogue **1′a** remained fruitless. The reduction of the diastereomeric imine **1′b** led to the diastereomer **5′b** whose newly created stereogenic center possessed the same configuration as for **5b** (Entries 9–12 versus entries 4–7). According the reducing agents used, the diastereoselective excess was found to be highly dependent of the chiral imine configuration.

After hydrogenolysis step and subsequent cyclisation of a diastereomerically enriched aminoester **5b** fraction (de 56%), the corresponding lactam **6** was analyzed by one and two dimensional ^1H NMR experiments (Scheme 2). NOESY and COSY correlations along with a "W" long range coupling between the equatorial hydrogen atom borne by the (C3) carbon atom and the hydrogen atom borne by the tertiary (C4) chiral center ascertained the absolute configuration (*2S*, 1′*S*) of the major aminoester diastereomer **5a-b** but also for **5′b**, giving the same lactam **6**.

By opposition to the ketoester derivatives, the reduction of the iminoesters provided inversion of the diastereoselectivity and the *anti* aminoesters became the major diastereomers. Consequently, chelated intermediates formation appeared far less efficient for iminoesters **1a-b** than for ketoesters **2a-c**.



Scheme 3. Matched and mismatched effect on Non Chelated Felkin Anh Intermediate **1b** and **1′b**.

This is in contradiction with previous results described in the literature but nevertheless for less hindered imino and enaminoesters.[34,36] In our case, the stereochemical outcome of the reduction reaction affording the major anti diastereomer **5a-b** could be explained assuming a predominantly non chelated Felkin Anh model: the presence of both hindered methylbenzyl moiety on the imino group and the quaternary carbon atom in the α-position prevents the formation of the cyclic chelated intermediate. Furthermore, with bulkier reducing agents, we observed a matched pair effect in the (*R,S*)-diastereomer **1′b** (Entries 7 and 8 versus 11 and 12) which became a mismatched effect with chelating reducing agent (Entry 5 versus 10) (Scheme 3). So, the action of L-selectride or lithium tri-*tert*-butoxyaluminium hydride applied to **1′b** allowed the access to aminoester **5b** with the best diastereomeric excesses up to 68%. In the situation of the bulkiest reducing agents, the supplementary *R*-stereocenter borne by the imino group efficiently overrides the influence of the *S*-stereocenter in the substrate: starting from **1′b**, the selectivity is dramatically increased in favor of **5′b** (matched case), while with the diastereomer **1b**, the Felkin and the anti-Felkin products are formed in near equivalent ratio (mismatched case). As depicted in Scheme 3, only the seemingly equivalent steric hindrance of the methyl and the alkyl chain could explain the matched and mismatched conformations.

CONCLUSION

In conclusion, we have studied the influence of a α-quaternary chiral carbon atom on the reduction of β-keto and β-iminoesters. This work constitutes the first experimental study of reduction of β-iminoesters bearing a α-quaternary stereocontrolled center. We have shown that diastereoselectivity could be inverted starting from β-iminoesters instead of β-ketoesters, with modest to good diastereoselectivity. Starting from chiral β-iminoesters, we showed that matched/mismatched effect using an additional stereogenic center was highly dependant of the nature of the reductant. Investigations of this matched/mismatched effect with bulkier chiral amines on asymmetric induction are ongoing.

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