Methylenation and Oxidation of Chiral Non-Racemic 2-Piperidones: Reactivity of a New 3-Oxolactam

Pilar Forns,[a] M. Montserrat Fernández,[a] Anna Diez,*[a] Mario Rubiralta,[a] Marie Pierre Cherrier,[b] Martine Bonin,[b] Jean-Charles Quirion[b]

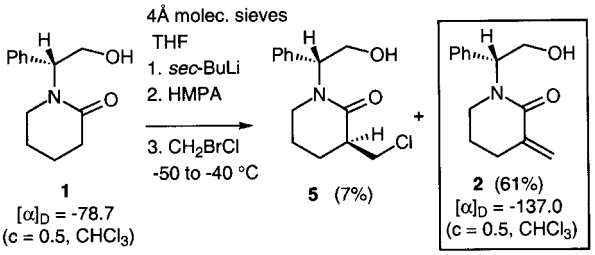
[a] Laboratori de Química Orgànica, Facultat de Farmàcia, Universitat de Barcelona, 08028-Barcelona, Spain
Fax: +34(93)4021896; E-mail: adiez@farmacia.far.ub.es

[b] Laboratoire de Chimie Thérapeutique, Faculté des Sciences Pharmaceutiques et Biologiques, Université René Descartes (Paris V), 4, Avenue de l'Observatoire, 75270 Paris Cédex 06, France

Received 22 May 1998; revised 17 July 1998

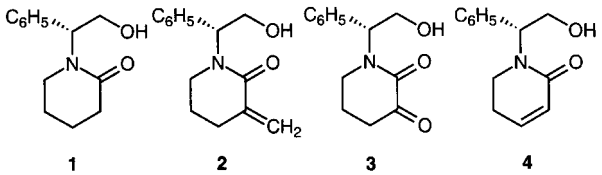
Abstract: The preparation of (*R*)-*N*-(2-hydroxy-1-phenylethyl)-3-methylenepiperidin-2-one (**2**) and (*R*)-*N*-(2-hydroxy-1-phenylethyl)piperidine-2,3-dione (**3**) from the (*R*)-phenylglycinol-derived lactam **1** is described. We have also studied the reactivity of 3-oxolactam **3**, and a series of functionalized derivatives has been prepared.

Key words: 3-methylenelactam, 3-oxolactam, 3-hydroxylactam, (*R*)-(–)-phenylglycinol, Wadsworth–Emmons Reaction



Scheme 1

In our earlier work, we investigated the reactivity of the enolate of chiral lactam **1** for the preparation of some 3-substituted piperidines.[1–3] During this study we encountered difficulties in introducing functionalized electrophiles. In order to circumvent this problem, we now describe the synthesis of 3-methylenelactam **2** and the oxolactam **3**. These new derivatives can be used as building blocks for the synthesis of more complex piperidine molecules: 3-methylenelactam **2** is a suitable substrate for conjugate addition in analogy with our previous work on the preparation of indole alkaloids from lactam **4**,[4] and oxolactam **3** is a precursor of C-3 and/or C-4 functionalized piperidines, as shown by the studies on its reactivity.



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

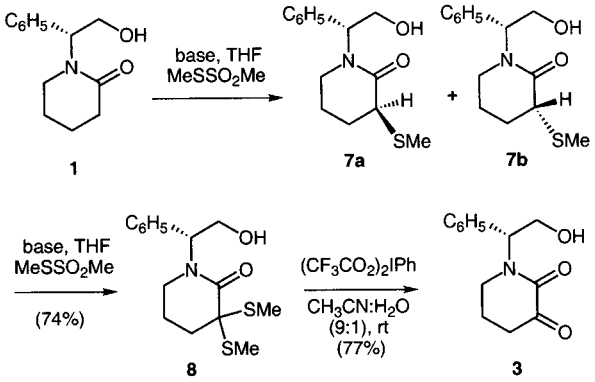
The synthesis of methylene lactam **2** from lactam **1** was first attempted through an elimination of the products of both hydroxymethylation followed by tosylation,[5] and reaction with Eschenmoser's salt followed by quaternization.[6] Since these methods were unsuccessful, we tried the direct methylenation of lactam **1** to obtain **2**. Thus, treatment of lactam **1** with *sec*-BuLi in the presence of hexamethylphosphoramide (HMPA) and 4Å molecular sieves, followed by addition of excess CH_2BrCl, yielded the 3-methylenelactam **2** together with a small proportion of the intermediate 3-chloromethyl lactam **5**[7] (Scheme 1).

Methylene lactam **2** was characterized by a molecular peak at *m/z* 231 in its mass spectrum, a double bond absorption in the IR spectrum at 1592 cm^{-1}, the presence of two olefin doublets (J_{AB} = 2 Hz) at δ = 5.35 and 6.28 in the ^1H NMR spectrum, and a methylene carbon at δ = 122.6 in the ^{13}C NMR spectrum. The chloromethyllactam **5** was obtained as a single isomer, which we assumed had an *S* configuration according to the model we proposed previously.[1] In its ^1H and ^{13}C NMR spectra, the chloromethyllactam **5** showed a multiplet at δ = 4.05–4.20 corresponding to the exocyclic methylene protons, and the methine and methylene carbons at δ = 43.8 (C-3) and 46.8 (CH_2Cl).

Simultaneously, methylenation of lactam **1** to give 3-methylenelactam **2** was attempted by transformation of 3-oxolactam **3** by a Wittig-type reaction[8] or using Lombardo's method.[9] In addition, we intended to use oxolactam **3** for further functionalization on positions C-3 and C-4.

The direct oxidation of a six-membered lactam to the corresponding 3-oxolactam has been described recently by forming the enolate with LDA and quenching with oxygen.[10,11] Before that, Meyers had prepared a five-membered chiral 3-oxolactam by oxidative cleavage of a dithioacetal.[12] Because of our experience in using Stork's method[13] to transform dithiane rings into carbonyls,[4b,14] we planned to prepare the 3-oxolactam **3** from the dimethyldithioacetal precursor **8**. Thus, reaction of lactam **1** with methyl methanethiolsulfonate was conducted in diverse experimental conditions as summarized in the Table. When we used *sec*-BuLi at –78 °C, a mixture of lactams **7a,b** was obtained in only very low yield (Entry 1). Use of a larger excess of base and electrophile improved the yield moderately, and the proportion of thioethers **7a** and **7b** after column chromatography was 6:4

(de 20%). In contrast, with LDA as the base at 0 °C (Meyers conditions), compounds **7** were obtained in 73% yield, with the diastereomeric excess increased to 80% (Entry 3). However, under these conditions the formation of dithioacetal **8** was already observed, in 13% yield. A second addition of base and nucleophile to the reaction medium, followed by stirring at room temperature, gave exclusively the dithioacetal **8** in 74% yield (Entry 4). Oxidation of dithioacetal **8** with $(CF_3COO)_2IPh$ in 90:10 acetonitrile/H_2O[12] provided the expected piperidin-2,3-dione **3** in 77% yield, as white crystals (Scheme 2). The structure assignment was confirmed by the analytical data, and in particular by the presence of two distinct carbonyl signals in the ^{13}C NMR spectrum at δ = 159.0 (lactam) and 191.7 (ketone).

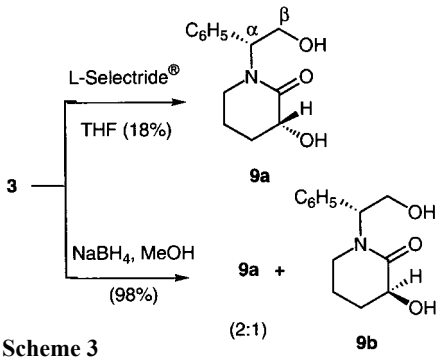


Scheme 2

We then performed a series of experiments to verify that the 3-oxo group of compound **3** reacted as an independent ketone function. This allowed us to prepare a series of derivatives with potential synthetic applicabilities.

We had tried unsuccessfully to prepare hydroxylactams **9** by electrophilic hydroxylation using Davis' oxaziridines.[15] However, treatment of oxolactam **3** with $NaBH_4$ yielded an unseparable 2:1[16] C3-diastereomeric mixture of hydroxylactams **9a,b** in 98% yield (Scheme 3). Both hydroxylactams were characterized by their C-3 methine carbon, which appeared at δ = 68.3 for **9a** (major isomer) and at δ = 68.0 for **9b** in the ^{13}C NMR spectrum of the mixture. In the ^1H NMR spectrum, both isomers presented the 3-H signal masked under the multiplet at δ = 4.10–4.25 that corresponds to the β-protons.

In order to improve the steric outcome of the reduction we tried using lithium tri-*sec*-butylborohydride (L-Selectride) at room temperature. In this case only isomer **9a** was obtained as a solid after column chromatography (silica gel) in 18% yield. The structure of isomer **9a** was confirmed by X-ray crystallography as the expected (α*R*,3*R*) isomer (Figure).



Scheme 3

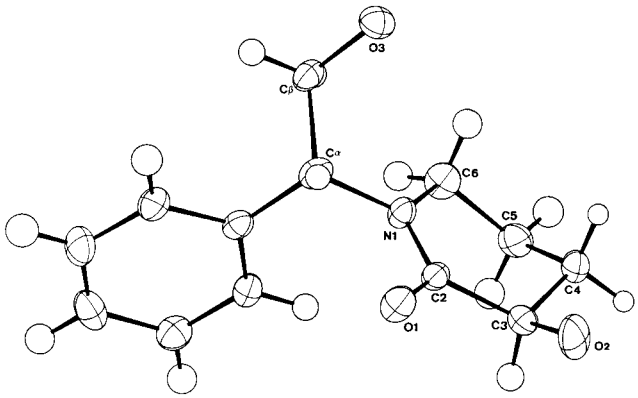


Figure ORTEP representation of the 3-hydroxylactam **9a**

The third kind of reaction we were interested in was the Wittig-type, for preparation of not only 3-methylene lactam **2** but also of the conjugated esters accessible from **3** by a Wadsworth–Emmons reaction.[17] When compound **3** was reacted with methylenetriphenylphosphonium ylide[18] the starting substrate was partially recovered together with unidentified decomposition products. The same result was obtained by treatment of lactam **3** with CH_2I_2 in the presence of Zn and $AlCl_3$ (Lombardo's method).[9a,19]

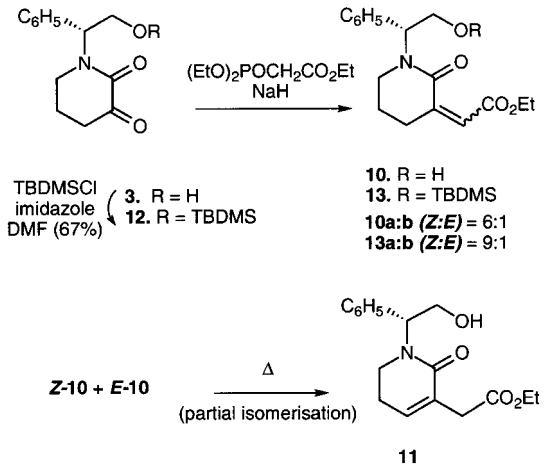
Treatment of oxolactam **3** in 1,2-dimethoxyethane (DME) with 2 equivalents of methylenetriphenylphosphonium ylide provided a mixture of *(Z)*-**10a** and *(E)*-**10b**. However, the excess phosphonoacetate had to be removed by mi-

Table Effects of Base and Temperature on the Formation of Compounds **7** and **8**

Entry	Temp (°C)	Base (equiv)	Electrophile (equiv)	Yield (%) **7a** + **7b**	Ratio of **7a**:**7b**[a]	Yield (%) **8**
1	–78	*sec*-BuLi (3.5)	3	11	60:40	–
2	–78	*sec*-BuLi (7)	6	27	60:40	–
3	0	LDA (3.5)	2.5	73	90:10	13
4	0, then 25	LDA (3, then 3.5)	3, then 3	0	–	74

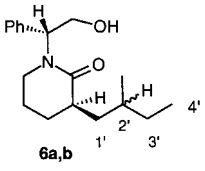
[a] Determined by ^1H NMR spectral analysis.

crodistillation, following which we observed the presence of a third compound, **11** (**10a**:**10b**:**11** = 6:1:1.8). Piperidinone **11** was the result of the double bond isomerization under the distillation conditions (Scheme 4). Subsequent column chromatography yielded pure **10a** and a mixture of **10b** and **11**. The most characteristic ^{1}H NMR datum of compounds **10** was the narrow triplet (J = 1 Hz) corresponding to the exocyclic olefin proton, which resonated at δ = 6.00 in the major *Z* isomer and at δ = 7.00 in the minor *E*-isomer. In contrast, compound **11** showed the 4-H olefin proton at δ = 6.40 and a singlet at δ = 3.30 due to the exocyclic methylene protons.



Scheme 4

In order to diminish the amount of phosphonoacetate needed and to facilitate the purification, we protected the hydroxy group of **3** by reaction with TBDMSCl under the standard conditions. The silyl ether **12** was then submitted to the Wadsworth–Emmons reaction with one equivalent of the ylide in dioxane and the conjugated esters **13a,b** were obtained. In this case, direct purification of the reaction mixture by column chromatography allowed the isolation of the pure isomers, and the diastereoselection was improved to **13a:13b** = 9:1 (52% total yield).



6a,b

In summary we have described the preparation of compounds **2** and **3** as the first examples of a family of C-3 functionalized lactams and show that the C-3 position of compound **3** reacts as a classical carbonyl group. The reactivity of these compounds to synthesize asymmetric C-4 substituted piperidines is under investigation.

Melting points were determined in a capillary tube on a Büchi apparatus. Optical rotations were measured with a Perkin-Elmer 241 polarimeter, at 23 °C. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini-200 instrument (200 MHz) and 2D NMR COSY experiments were performed on a Varian XL-500 instrument (500 MHz). Unless otherwise noted, NMR spectra were registered in $CDCl_3$, and chemical shifts are expressed in parts per million (δ) relative to internal TMS. IR spectra were recorded on a Nicolet FT-IR spectrophotometer. Mass spectra were determined on a Hewlett-Packard 5988A mass spectrometer, either by chemical ionization (CIMS) or electronic impact (EIMS). Flash column chromatography was carried out on silica gel 60 (40–63 mm, SDS). TLC was performed on silica gel 60 (F254, Macherey-Nagel) and developed with the solvent described in each case for flash chromatography. The spots were located by UV light and Draggendorf or hexachloroplatinate reagent. Purification of reagents and solvents was effected according to standard methods. Prior to concentration under reduced pressure, all extracts were dried (Na_2SO_4). Microanalyses were performed on a Carlo Erba 1106 analyzer by the Departament de Química Orgànica i Biològica CID, Barcelona. The X-ray analysis of compound **9a** was performed at the Faculty of Pharmacy of the Université de Paris V, Paris.

(α*R*)-*N*-(2-Hydroxy-1-phenylethyl)-3-methylenepiperidin-2-one (2)

To a solution of lactam **1** (718 mg, 3.27 mmol) in anhyd THF (20 mL) containing 4Å molecular sieves (5 g) was added *sec*-BuLi (1.3M, 7.5 mL, 8.25 mmol) at –78 °C under a N_2 atmosphere, and the mixture was stirred for 15 min. HMPA (1.4 mL, 8.25 mmol) was then added at –60 °C, immediately followed by CH_2BrCl (1.1 mL, 16.35 mmol), and the mixture was stirred for 3 h at –40 °C. The reaction was quenched by the addition of sat. aq NH_4Cl solution (20 mL) and the product was extracted with EtOAc. The organic extracts were dried and evaporated to give a pale brown oil which was chromatographed (EtOAc/hexane, 7:3) to separate the 3-methylenelactam **2** and 3-chloromethyllactam **5**.

3-Methylenelactam 2

Yield 61%; white solid; $[\alpha]_D$ –137.7 (c = 0.5, $CHCl_3$); mp 104–106 °C (EtOAc).

IR ($CHCl_3$): ν = 3450–3350, 1651, 1592 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ = 1.55–1.95 (m, 3 H, 5-H and OH), 2.45–2.65 (m, 2 H, 4-H), 3.03 (ddd, 1 H, J = 12, 8, 4 Hz, 6-H_A), 3.30 (ddd, 1 H, J = 12, 7, 4 Hz, 6-H_B), 4.10–4.30 (m, 2 H, CH_2OH), 5.35 (d, 1 H, J = 2 Hz, =CH_A), 5.85 (dd, 1 H, J = 9, 5 Hz, α-H), 6.28 (d, 1 H, J = 2 Hz, =CH_B), 7.20–7.55 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$/TMS): δ = 23.0 (C-5), 29.6 (C-4), 44.0 (C-6), 58.9 (C-α), 61.5 (C-β), 122.6 (=CH_2), 127.7 and 128.6 (Ph-*o*, Ph-*m*, Ph-*p*), 136.9 and 137.6 (Ph-*i* and C-3), 165.8 (C-2).

EI-MS: *m/z* (%) = 231 (M^+, 0.1), 213 ($M^+ - H_2O$, 19), 200 (100).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.79; H, 7.42; N, 6.06. Found: C, 72.72; H, 7.34; N, 5.93.

(α*R*,3*R*)-3-Chloromethyl-*N*-(2-hydroxy-1-phenylethyl)piperidin-2-one (5)

Yield 7%.

^{1}H NMR ($CDCl_3$/TMS): δ = 1.65–2.02 (m, 4 H, 4-H and 5-H), 2.80–2.95 (m, 2 H, 3-H and 6-H_A), 3.10–3.22 (m, 1 H, 6-H_B), 3.70 (br s, 1 H, OH), 3.80 (dd, 1 H, J = 12, 2 Hz, CH_AOH), 4.05 (dd, 1 H, J = 12, 9 Hz, CH_BOH), 4.06–4.20 (m, 2 H, CH_2Cl), 5.85 (dd, 1H, J = 9, 2 Hz, α-H), 7.20–7.40 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$/TMS): δ = 21.6 (C-5), 24.2 (C-4), 43.8 (C-3), 43.9 (C-6), 46.7 (CH_2Cl), 58.9 (C-α), 61.4 (C-β), 127.7, 128.5 and 128.6 (Ph-*o*, Ph-*m*, and Ph-*p*), 136.4 (Ph-*i*), 170.9 (C-2).

EI-MS: *m/z* (%) = 269 (M^+ + 1.5, 0.2), 267 (M^+ – 0.5, 0.6), 249 (27), 200 (100).

In the absence of molecular sieves (α*R*,3*S*,2'*RS*)-*N*-(2-hydroxy-1-phenylethyl)-3-(2-methylbut-1-yl)piperidin-2-ones **(6a,b)** were also formed besides the lactams **2** and **5**.

^{1}H NMR (pure **6a**, $CDCl_3$/TMS, 500 MHz): δ = 0.89 (t, 3 H, *J* = 7 Hz, CH_3CH$_2$), 0.92 (d, 3 H, *J* = 7 Hz, CH_3CH), 1.0–51.55 (m, 4 H, 5-H and 3'-H), 1.65–2.00 (m, 4 H, 2'-H and 1'-H_A), 2.40–2.51 (m, 1 H, 1'-H_B), 2.87 (ddd, 1 H, *J* = 12, 8, 5 Hz, 6-H_A), 3.15–3.25 (m, 2 H, 6-H_B and 3-H), 4.10–4.20 (br s, 2 H, CH_2OH), 5.70 (t, 1 H, *J* = 6 Hz, α-H), 7.20–7.40 (m, 5 H, C_6H_5).

^{13}C NMR (1:1 mixture of **6a:b**, $CDCl_3$/TMS): δ = 11.0 and 11.5* (CH_3CH$_2$), 18.1* and 19.7 (CH_3CH), 21.4 (C-5), 25.7* and 26.4 (CH$_3$CH_2), 28.0 and 30.4* (C-4), 31.5* and 31.6 (CH$_3$CH), 39.1* and 39.6 (CH_2CH), 39.7 (C-3), 44.0 and 44.1* (C-6), 59.3 and 59.4* (C-α), 62.2 (C-β), 127.7, 127.8, and 128.6 (Ph-*o*, Ph-*m*, and Ph-*p*), 136.9 (Ph-*i*), 175.6 (C-2).

EI-MS: *m/z* (%) = 289 (M^+, 0,1), 258 (100).

(α*R*,3*RS*)-*N*-(2-Hydroxy-1-phenylethyl)-3-methylsulfanylpiperidin-2-ones (7a,b)

To a solution of the lactam **1** (82 mg, 0.375 mmol) in anhyd THF (4 mL) under N_2 atmosphere was added LDA (1.4M, 1.31 mmol, 858 mL) at 0 °C. The mixture was stirred for 25 min. $MeSSO_2Me$ (0.75 mmol, 97 mL) was added and the mixture was stirred at 0 °C for 30 min. The reaction was quenched by adding satd aq NH_4Cl solution (2 mL) and the crude was extracted with EtOAc. The organic extracts were dried and evaporated to yield a brown oil which was chromatographed. On elution with EtOAc/hexane (80:20) dithioacetal **8** (13%, see below) was obtained. Elution with EtOAc gave pure methylsulfanyllactam **7b** (7%) and EtOAc/MeOH (95:5) as eluent afforded the isomer 7a (66%).

7a: white solid; $[\alpha]_D$ –171.4 (*c* = 0.78, $CHCl_3$); mp 126–127 °C (EtOAc).

IR ($CHCl_3$): ν = 3345, 1620 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.70–1.80 (m, 1 H, 5-H_A), 1.85–2.00 (m, 2 H, 5-H_B and 4-H_A), 2.20–2.30 (m, 1 H, 4-H_B), 2.35 (s, 3 H, SCH_3), 2.84 (dd, 1 H, *J* = 7, 4 Hz, OH), 3.00 (dt, 1 H, *J* = 12, 6 Hz, 6-H_A), 3.19 (ddd,1 H, *J* = 12, 8, 4 Hz, 6-H_B), 3.45 (t, 1 H, *J* = 5,1Hz, 3-H_A), 4.05–4.25 (m, 2 H, β-H), 5.75 (dd, 1 H, *J* = 12 and 4 Hz, α-H), 7.20–7.40 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$/TMS): *d* = 16.4 (CH_3), 20.5 (C-5), 27.8 (C-4), 43.5 (C-6), 45.9 (C-3), 58.9 (C-α), 61.8 (C-β), 127.6, 127.8 and 128.6 (Ph-*o*, Ph-*m,* and Ph-*p*), 136.7 (Ph-*i*), 171.2 (C-2).

CI-MS: *m/z* = 266 (M^++1).

Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.21; N, 5.27; S, 12.08. Found : C, 63.46; H, 7.28; N, 5.34; S, 12.06.

7b: $[\alpha]_D$ –35.0 (*c* = 0.48, $CHCl_3$).

^{1}H NMR ($CDCl_3$/TMS,300 MHz): δ = 1.57–1.70 (m, 1 H, 5-H_A), 1.80–2.20 (m, 3 H, 4-H and 5-H_B), 2.32 (s, 3 H, SCH_3), 3.00 (dt, 1 H, *J* = 12, 6 Hz, 6-H_A), 3.10 (br s, 1 H, OH), 3.29 (dt, 1 H, *J* = 12, 6 Hz, 6-H_B), 3.45 (t, 1 H, *J* = 6 Hz, 3-H), 4.13 (d, 2 H, *J* = 9 Hz, β-H), 5.71 (t, 1 H, *J* = 9 Hz, α-H), 7.20–7.40 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$/TMS): δ = 16.0 (SCH_3), 20.8 (C-5), 27.4 (C-4), 43.4 (C-6), 46.0 (C-3), 59.3 (C-α), 61.7 (C-β), 127.6 (Ph-*o* and Ph-*p*), 128.6 (Ph-*m*), 136.7 (Ph-*i*), 170.9 (C-2). 5:5)

(α*R*)-*N*-(2-Hydroxy-1-phenylethyl)-3,3-dimethyldisulfanylpiperidin-2-one (8)

To a solution of the lactam **1** (280 mg, 1.28 mmol) in anhyd THF (25 mL), at 0 °C under N_2 atmosphere was added LDA (1.2 M, 3.7 mL, 4.47 mmol) at 0 °C under a N_2 atmosphere. After stirring for 30 min, $MeSSO_2Me$ (0.46 mL, 4.48 mmol) was added. After 1 h at 0 °C the manipulation was repeated by adding LDA (1.2 M, 3.7 mL, 4.47 mmol) and $MeSSO_2Me$ (0.46 mL, 4.48 mmol), and the mixture was stirred at r.t. for 2 h. The reaction was quenched by the addition of aq NH_4Cl solution (20 mL) and the product was extracted with EtOAc. The organic extracts were dried and evaporated to yield a brown oil, which after column chromatography (EtOAc/hexane, 6:4) furnished the dithioacetal **8** (74%) as a pale yellow solid; $[\alpha]_D$ –96.1 (*c* = 0.88, $CHCl_3$); mp 100.0–100.3 °C (EtOAc/hexane).

^{1}H NMR ($CDCl_3$/TMS): δ = 1.92 (m, 2 H, 5-H), 2.17 and 2.19 (2 s, 3 H each, SCH_3), 2.20–2.30 (m, 2 H, 4-H), 2.55 (t, 1 H, *J* = 6 Hz, OH), 3.02 and 3.27 (2 dt, 1 H each, *J* =12, 6 Hz, 6-H), 4.05–4.20 (m, 2 H, CH_2OH), 5.67 (dd, 1 H, *J* = 9, 6 Hz, α-H), 7.20–7.40 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$/TMS): δ = 12.9 and 13.1 (SCH_3), 20.1 (C-5), 34.9 (C-4), 43.9 (C-6), 50.0 (C-3), 59.6 (C-α), 61.8 (C-β), 127.6, 127.8, and 128.8 (C_6H_5), 169.5 (C-2).

CI-MS: *m/z* = 312 (M^+ + 1), 340 (M^+ + 29).

Anal. Calcd for $C_{15}H_{21}NO_2S_2$: C, 57.84; H, 6.79; N, 4.49. Found: C, 57.34; H, 6.77; N, 4.48.

(α*R*)-*N*-(2-Hydroxy-1-phenylethyl)piperidine-2,3-dione (3)

To a solution of **8** (533 mg, 1.71 mmol) in MeCN/H_2O (9:1, 70 mL) was added $(CF_3CO_2)_2$IPh (3.42 mmol, 1.84 g) and the mixture was stirred at r.t. for 3 h. The reaction was quenched by the addition of aq sat. $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were dried and evaporated to afford a pale yellow oil which was chromatographed (CH_2Cl_2/MeOH, 95:5) to obtain the oxolactam **3** (77%) as a white solid; $[\alpha]_D$ –169.0 (*c* = 0.51, $CHCl_3$); mp 167 °C (EtOAc).

IR ($CHCl_3$): ν = 3367, 1736, 1673 cm^{-1}.

^{1}H NMR (DMSO-d_6/TMS): δ = 1.90–2.10 (m, 2 H, 5-H), 2.65 (t, 2 H, *J* = 7 Hz, 4-H), 3.16–3.30 (m, 1 H, 6-H_A), 3.50–3.62 (m, 1 H, 6-H_B), 4.10–4.22 (m, 2 H, CH_2OH), 5.00 (t, 1 H, *J* = 6 Hz, OH), 5.85 (dd, 1 H, *J* = 9, 5 Hz, α-H), 7.20–7.40 (m, 5 H, C_6H_5).

^{13}C NMR (DMSO-d_6/TMS): δ = 21.6 (C-5), 38.1 (C-4), 42.9 (C-6), 59.2 (C-α), 60.9 (C-β), 127.7, 128.2, and 128.8 (Ph), 135.7 (Ph-*i*), 159.0 (C-2), 191.7 (C-3).

CI-MS: *m/z* = 234 (M^++1).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.00. Found: C, 66.51, H, 6.51; N, 5.88.

3-Hydroxy-*N*-(2-hydroxy-1-phenylethyl)piperidin-2-ones (9a,b)

Method A: To a solution of **3** (100mg, 0.42 mmol) in anhyd THF (5 mL) at 0 °C was added $NaBH_4$ (75 mg, 6.81 mmol) portionwise. After 2 h at r.t., H_2O was added (3 mL) and the mixture was extracted with CH_2Cl_2. The organic extracts were dried and evaporated to give a 2:1 diastereomeric mixture of the unseparable alcohols **9a/9b** (98%).

Method B: To a solution of **3** (86 mg, 0.37 mmol) in anhyd THF (5mL) cooled at –78 °C was added slowly L-Selectride (1 M, 0.74 mL, 0.74 mmol). The mixture was stirred for 2 h at –78 °C and for 1 h at r.t. To quench the reaction THF (5 mL), HOAc (1.5 mL), and H_2O (2 mL) were added. The aqueous phase was extracted with EtOAc (3 × 5 mL). The organic layers were dried and evaporated, and the residue was chromatographed (EtOAc) to yield **9a** (19%).

IR ($CHCl_3$): ν = 3017, 1677 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ = 1.60–2.00 (m, 3 H, 5-H and 4-H_A), 2.20–2.30 (m, 1 H, 4-H_B), 2.98–3.10 (m, 1 H, 6-H_A), 3.20–3.30 (m, 1 H, 6-H_B), 4.10–4.25 (m, 3 H, 3-H and β-H), 5.65 (dd, 1 H, *J* = 8, 6 Hz, α-H), 7.20–7.50 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$/TMS): δ = 20.0 (C-5), 28.1 (C-4), 43.1(C-6), 59.1 (C-α), 61.3 (C-β), 68.3 (C-3), 127.5, 127.7, and 128.7 (C_6H_5), 138.7(Ph-*i*), 174.0 (C-2).

CI-MS: *m/z* = 236 (M^++1), 264 (M^++29).

X-Ray Crystallography of Lactam 9a

Crystal data : $C_{13}H_{15}NO_3$. M_w = 233.27. A suitable crystal was investigated on a Siemens P3 diffractometer [λ(Mo Kα radiation) = 0.71069 Å, graphite monochromator]. Orthorhombic, space group $P2_12_12_1$, Z = 4, a = 7.832 (4) Å, b = 8.975 (9) Å, c = 16.801 (9) Å, dc = 1.31 g.cm^{-3}; F(000) = 496, μ = 0.87 mm^{-1}. 1668 reflections up to 2θ = 55° of which 667 with F =3σ(F) were kept in refinement calculations. The structure was solved by direct methods using SHELXS86[20] and refined by the full matrix least squares based on F with CRYSTALS.[21] All non-hydrogen atoms were located in difference Fourier maps and refined at observed positions with anisotropic temperature factors. Convergence was reached at $R = \Sigma(F_o - F_c)/\Sigma F_o = 0.041$. Molecular graphics are from CAMERON.[22]

(α*R*)-3-(Ethoxycarbonylmethylene)-*N*-(2-hydroxy-1-phenylethyl)piperidin-2-one (10)

To a suspension of NaH (55%, 40 mg, 0.903 mmol) in DME (3 mL) was added triethyl phosphonoacetate (179 mL, 0.903 mmol). When the mixture was clear, a solution of **3** (100 mg, 0.43 mmol) in warm DME (3 mL) was added and the mixture was refluxed for 2 h. After cooling to r.t., sat. aq NH_4Cl (5 mL) was added and the aqueous phase was extracted with CH_2Cl_2. The organic extracts were dried and evaporated. The excess of triethylphosphonoacetate was removed from the residue by distillation (155–160 °C/8–9 Torr). The crude product was chromatographed (EtOAc) to isolate isomer (*E*)-**10a** (5%) and a mixture of (*Z*)-**10b** and **11** (45%).

Isomer (*E*)-10b

^{1}H NMR ($CDCl_3$/TMS, 200 MHz): δ = 1.30 (t, 3 H, *J* = 7 Hz, CH_3), 1.70–1.98 (m, 2 H, 5-H), 2.50–2.63 (m, 1 H, 4-H_A), 3.00–3.20 (m, 2 H, 4-H_B and 6-H_A), 3.20–3.40 (m, 1 H, 6-H_B), 4.05–4.35 (m, 4 H, β-H and CH_2O), 5.90 (dd, 1 H, *J* = 8, 7 Hz, α-H), 7.02 (br s, 1 H, $W_{1/2}$ = 8 Hz, =CH), 7.20–7.40 (br s, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$/TMS): δ = 16.2 (CH_3), 24.0 (C-5), 35.6 (C-4), 41.5 (C-6), 58.7 (C-α), 62.2 and 62.3 (C-β and C*H*$_2$O), 126.8, 127.7 and 128.5 (C_6H_5), 135.9 (Ph-*i*), 136.5 (=CH), 163.5 (CO_2Et), 171.5 (C-2).

CI-MS: *m*/*z* = 304 (M^++1).

Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.32; H, 6.93; N, 4.62. Found: C, 67.01; H, 7.03; N, 4.62.

(α*R*)-*N*-[2-(*tert*-Butyldimethylsilyloxy)-1-phenylethyl]piperidine-2,3-dione (12)

To a solution of **3** (231 mg, 0.991 mmol) in anhyd DMF (2.5 mL) and imidazole (135 mg, 1.98 mmol) was added a solution of TBDMSCl (135 mg, 1.24 mmol) in DMF (1 mL). The mixture was stirred overnight at r.t. and quenched with brine (4 mL). The aqueous phase was extracted with Et_2O, and the organic extracts were dried and evaporated, to give an oil which was chromatographed (EtOAc/cyclohexane, 2:8 to 1:1) to yield **12** (52%); $[\alpha]_D$ –26.0 (*c* = 0.1, MeOH).

^{1}H NMR ($CDCl_3$/TMS): δ = 0.10 (2 s, 6 H, $SiCH_3$), 0.90 (s, 9 H, C*C*H$_3$), 2.00–2.10 (m, 2 H, 5-H), 2.70–2.80 (m, 2 H, 4-H), 3.30 (m, 1 H, 6-H_A), 3.55 (m, 1 H, 6-H_B), 4.20 (m, 2 H, β-H), 5.80 (t, 1 H, *J* = 5 Hz, α-H), 7.20–7.50 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$/TMS): δ = 0.0 ($SiCH_3$), 21.9 (C*C*H$_3$), 25.7 (C-5), 38.4 (C-4), 43.5 (C-6), 57.9 (C-α), 61.4 (C-β), 127.6, 127.9, and 128.6 (C_6H_5), 138.4 (Ph-*i*), 158.0 (C-2), 191.8 (C-3).

CI-MS: *m*/*z* = 348 (M^+ + 1).

(α*R*)-*N*-(2-*tert*-Butyldimethylsilyloxy-1-phenylethyl)-3-(ethoxycarbonylmethylene)piperidin-2-ones (13a,b)

To a suspension of NaH (55%, 15 mg, 0.325 mmol) in dioxane (1.5 mL) was added triethylphosphonoacetate (65 mL, 0.325 mmol). When the mixture was clear, a solution of silylated lactam **12** (113 mg, 0.325 mmol) in dioxane (2 mL) was added. The mixture was stirred for 3 h at r.t. The reaction was quenched by the addition of sat. aq $NaHCO_3$ solution and extracted with EtOAc. The organic extracts were dried and evaporated and the residue was flash chromatographed. On elution with cyclohexane, isomer (*E*)-**13b** (5%) was isolated pure and elution with cyclohexane/EtOAc (80:20) gave isomer (*Z*)-**13a**.

(*Z*)-**13a**: yield 47%; $[\alpha]_D$ –100.0 (*c* = 1.2, $CHCl_3$).

IR (film): ν = 1715, 1680 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ = 0.10 (s, 6 H, $SiCH_3$), 0.80 (s, 9 H, C*C*H$_3$), 1.30 (t, *J* = 7 Hz, 3 H, C*H*$_3$CH$_2$), 1.60–1.80 (m, 2 H, 5-H), 2.40–2.50 (m, 2 H, 4-H), 2.90–3.05 (m, 1 H, 6-H_A), 3.20–3.35 (m, 1 H, 6-H_B), 4.00–4.10 (m, 2 H, β-H), 4.30 (q, 2 H, *J* = 7 Hz, CH_2O), 5.75–5.80 (m 1 H, α-H), 5.95 (s, 1 H, =CH), 7.20–7.40 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$/TMS): δ = 1.0 and 1.3 ($SiCH_3$), 13.9 (CH_2CH_3), 17.9(C*C*H$_3$), 25.7 (C-5), 29.7 (C-4), 43.8 (C-6), 56.6 (C-α), 60.7, and 61.9 (C-β and CH_2O), 126.8, 127.8, and 128.2 (C_6H_5), 135.8 (Ph-*i*), 137.4 (=CH), 162.6 (CO_2Et), 167.9 (C-2).

CI-MS: *m/z* = 418 (M^++1).

(*E*)-**13b**: $[\alpha]_D$ –55.0 (*c* = 1.3, $CHCl_3$).

IR (film): ν = 1715, 1682 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ = 0.00 (s, 6 H, $SiCH_3$), 0.80 (s, 9 H, C*C*H$_3$), 1.30 (t, 3 H, *J* = 7 Hz, CH_2CH_3), 1.50–1.80 (m, 3 H, 5-H and 4-H_A), 2.90–3.00 (m, 1 H, 4-H_B), 3.00–3.15 (m, 1 H, 6-H_A), 3.30–3.50 (m, 1 H, 6-H_B), 4.00–4.17 (m, 2 H, β-H), 4.20 (q, 2 H, *J* = 7 Hz, CH_2O), 5.85 (dd, 1 H, *J* = 9, 7 Hz, α-H), 7.00 (br s, 1 H, =CH), 7.20–7.40 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$/TMS): δ = –0.05 ($SiCH_3$), 14.1 (CH_2CH_3), 22.3 (C*C*H$_3$), 25.7 (C-5), 29.6 (C-4), 43.6 (C-6), 58.0 (C-α), 60.2, and 61.8 (C-β and C*H*$_2$O), 123.7 (C-3), 127.5, 127.9, and 128.4 (C_6H_5), 137.1 (=CH), 161.0 (CO_2Et), 167.0 (C-2).

CI-MS: *m/z* = 418 (M^++1).

Acknowledgement

Support for this research has been provided by the CIRIT (Generalidad de Catalunya) through grants QFN95-4703 and 1995SGR-00429, and by the Ministerio de Educación y Ciencia through grant HF-312B. M.-P. Cherrier thanks ADIR (Servier) for financial support.

References

(1) Micouin, L.; Bonin, M.; Cherrier, M.-P.; Mazurier, A.; Tomas, A.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron* **1996**, *52*, 7719.
(2) (a) Micouin, L.; Quirion, J.-C.; Husson, H.-P. *Synthetic Commun*. **1996**, *26*, 1605.
(b) Micouin, L.; Varea, T.; Riche, C.; Chiaroni, A.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1994**, *35*, 2529.
(3) Rodriguez, R.; Estiarte, M.A.; Diez, A.; Rubiralta, M.; Colell, A.; Garcia-Ruiz, C.; Fernández-Checa, J.-C. *Tetrahedron* **1996**, *52*, 7727.
(4) (a) Micouin, L.; Diez, A.; López, I.; Rubiralta, M.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett*. **1995**, *36*, 1693–1696.

(b) For the synthesis of *Aspidosperma* alkaloids from a non-chiral 3-methylenelactam, see: Forns, P.; Diez, A.; Rubiralta, M. *J. Org. Chem*. **1996**, *61*, 7882.
(5) (a) Roush, W.R.; d'Ambra, T.E. *J. Am. Chem. Soc.* **1983**, *105*, 1058.
(b) De Clercq, P.; Vanderwalle, M. *J. Org. Chem.* **1977**, *42*, 3477.
(6) (a) Danishefsky, S.; Schuda, P.F.; Kitahara, T.; Etheredge, S.J. *J. Am. Chem. Soc.* **1977**, *99*, 6066.
(b) Roberts, J.L.; Borromeo, P.S.; Poulter, C.D. *Tetrahedron Lett.* **1977**, 1621.
(7) In the absence of molecular sieves, lactams **2** and **5** were obtained in variable yields, together with compound **6**. Compound **6** proved to be a mixture of only two diastereomers (**a,b**), identified by a molecular peak at *m/z* 289, and by the presence of two methyl groups and two methine carbons for each isomer in the spectral data of the mixture. Conjugate addition of *sec*-BuLi on methylenelactam **2** would presumably lead to the formation of the four possible isomers;[2b] therefore, compounds **6a,b** were assigned as the C-2' epimers resulting from the attack of *sec*-BuLi as a nucleophile on chlorolactam **5**. This also indicated that the variable yields we were obtaining resulted from the competition of the S_{N_2} reaction versus the elimination.
(8) For a review, see: Krief, A. *Tetrahedron* **1980**, *36*, 2531.
(9) (a) Hakan, K.; Thielmann, M.; Thielmann, T.; Winterfeldt, E. *Tetrahedron* **1987**, *43*, 2035.
(b) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2417.
(10) Li, W.; Hanau, C.E.; d'Avignon, A.; Moeller, K.D. *J. Org. Chem* **1995**, *60*, 8155.
(11) Moeller, K.D.; Li, W. *J. Am. Chem. Soc*. 1**996**, *118*, 10106.
(12) Meyers, A.I.; Sturgess, M.A. *Tetrahedron Lett*. **1988**, *29*, 5339.
(13) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.
(14) Forns, P.; Diez, A.; Rubiralta, M.; Solans, X.; Font-Bardia, M. *Tetrahedron* **1996**, *52*, 3563.
(15) (a) Davis, F.A.; Chen, B.-C. *J. Org. Chem.* **1993**, *58*, 1751.
(b) Davis, F.A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919.
(16) The proportion was determined from the ^{1}H NMR analysis.
(17) Diez, A.; Vila, C.; Sinibaldi, M.-E.; Troin, Y.; Rubiralta, M. *Tetrahedron Lett.* **1993**, *34*, 733.
(18) Hasan, I.; Marinelli, E.R.; Chang Lin, L.C.; Fowler, F.W.; Levy, A.B. *J. Org. Chem.* **1981**, *46*, 157.
(19) Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293.
(20) Sheldrick, G. M. (1985). SHELXS86. *Program for solution of Crystal Structures*. University of Göttingen, Germany.
(21) Watkin, D. J., Carruthers J. R. & Betteridge P. W., CRYSTALS-User Guide, Chemical Crystallography Laboratory, University of Oxford, England, 1985.
(22) Pearce, L. J., Watkin, D. J. & Prout, C. K., CAMERON : A Program for Plotting Molecular Structures, Chemical Crystallography Laboratory, University of Oxford, England, 1992.