Synthesis and crystal structure of (3*S*)-3-(1*H*-benzotriazol-1-yl)- and (3*S*)-3-benzenesulfonyl-2-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-2,3-dihydro-1*H*-isoindol-1-ones

Eric Deniau[a]*, Axel Couture[a], Pierre Grandclaudon[a] and Guy Nowogrocki[b]

[a]*UMR 8009 – COM, Laboratoire de Chimie Organique Physique, Université des Sciences et Technologies de Lille I, Bâtiment C3(2), F-59655 Villeneuve d'Ascq Cedex, France*

[b]*UMR 8012, Laboratoire de Cristallochimie et Physicochimie du Solide, ENSC Lille, Bâtiment C7, BP 108, 59652 Villeneuve d'Ascq Cedex, France*

Virtually diastereochemically pure 3-heterosubstituted isoindolinones have been obtained by nucleophilic addition on an *N*-acylhydrazonium salt generated by acidic treatment of the corresponding 3-hydroxy derivatives bearing a SMP type auxiliary and their structure has been assessed by single crystal X-ray analysis.

Keywords: stereoselection, 3-heterosubstituted isoindolinones

3-Heterosubstituted isoindolinones represent a class of polyheterocyclic systems which have attracted much attention from the scientific community since they represent the core unit of a wide range of biologically active compounds. In particular compounds heterosubstituted at C(3) (Fig. 1) such as thiazolidinone **1**[1] (HIV reverse transcriptase inhibitor), **2**[2] (antidiabetic, antiobesity) as well as the architecturally more sophisticated thiolactams **3**[3] (HIV integrase inhibitor) have been extensively studied. It has been also demonstrated that 3-amino derivatives such as **4**[4] are potent opioid receptor antagonist while compound **5**[5] displays tumour necrosis factor α inhibitor properties and **6**[6] has shown promising psychogeriatric activities. Surprisingly only few efforts have been devoted to the asymmetric synthesis of chiral 3-heterosubstituted isoindolinones even though it has been well established that the absolute configuration of the stereogenic centre at C(3) plays a crucial role for the biological activity.[7]

We then assumed that it should be interesting to develop a versatile methodology for the stereoselective incorporation of heterosubstituents, *e.g.* S and N, at the benzylic position of the lactam unit. We anticipated that this issue could be addressed by diastereoselective nucleophilic addition on an *N*-acyliminium species equipped with a chiral auxiliary and embedded in a preformed isoindolinone framework. Crucial for the success of this synthetic approach was to identify an easily incorporated stereocontrolling agent, sufficiently robust to support the creation of the highly reactive iminium ion and also to be easily removed without racemisation. The choice of the (*S*)-2-methoxymethyl-pyrrolidin-1-yl group (SMP) as the stereocontrolling agent was dictated on reliance with Kibayashi assumptions.[8] We assumed that high stereoselectivity could be obtained by facial selectivity attributable to the nucleophilic approach on the sterically less demanding face of the transition conformers **7a** or **7b** (Fig. 2) where the N-C(2) bond adopts a perpendicular position to the plane of the azomethine bond.

From a synthetic point of view[9] the generation of the *N*-acylhydrazonium ion **7a,b** was achieved as depicted in Scheme 1. Initially the hydroxyisoindolinone **8** was obtained by sequential deprotonation–halogen/metal interconversion applied to the bromobenzhydrazide **9** and subsequent interception of the dilithiated species with dimethylformamide. This operation delivered the hemiaminal **8** as a mixture of diastereomers, candidates for the generation of the required *N*-acylhydrazonium species **7**, with an excellent yield. This hydroxyisoindolinone was treated with *p*-toluenesulfonic acid, and with $PhSO_2H$ generated *in situ* or with benzotriazole, to provide the sulfonyl and benzotriazolyl derivatives, **10** and **11** respectively, with excellent yields and excellent diastereoselectivities (Scheme 1).

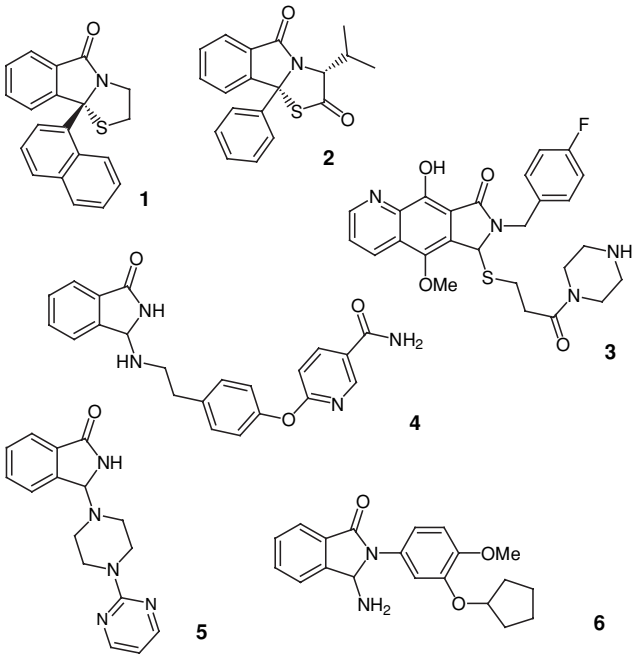


Fig. 1 Biologically active 3-heterosubstituted isoindolinones.

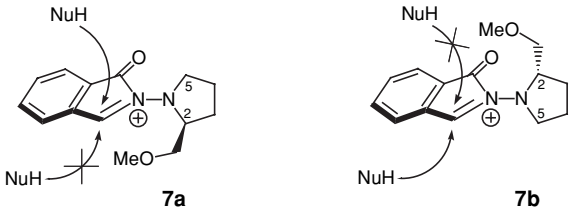
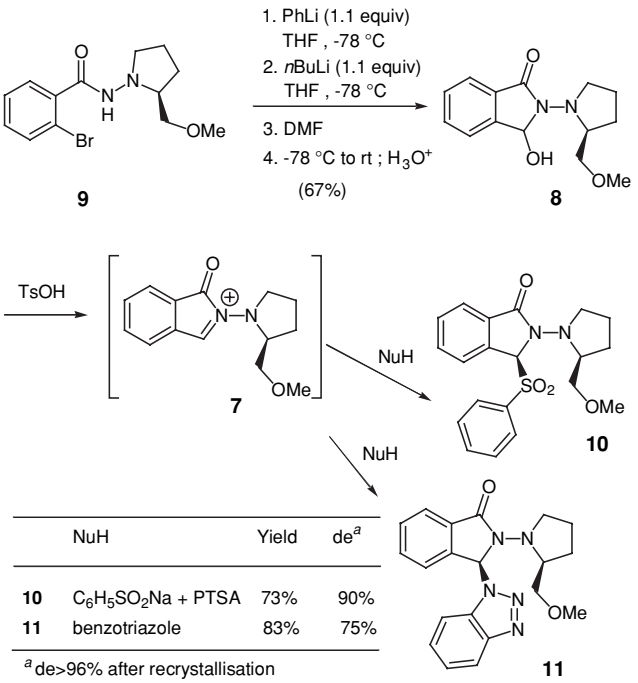


Fig. 2 Nucleophilic attacks on the transient *N*-acyliminium species.

For structural elucidation and hence for the assignment of the geometry of the transient intermediate involved in the chemical process, *i.e.* **7a** or **7b**, X-ray diffraction appeared a method of choice and we have therefore investigated the crystal structure of compounds **10**, **11**. For this purpose the title compounds were recrystallised from hexane–toluene.

The X-ray analysis allowed the unambiguous assignment of the (3*S*) configuration to both models (Figs 3 and 4). The high

* Correspondent. E-mail: eric.deniau@univ-lille1.fr



	NuH	Yield	de[a]
10	$C_6H_5SO_2Na$ + PTSA	73%	90%
11	benzotriazole	83%	75%

[a] de>96% after recrystallisation

Scheme 1 Synthesis of the 3-heterosubstituted models **10**, **11**.

stereoselectivity observed in these reactions may be ascribed to the anticipated antiperiplanar approach of the nucleophile preferentially from the sterically less hindered face thus leading exclusively to the (3*S*) isomers. Furthermore, one can reasonably assume that the preferred geometry for the transient *N*-acylhydrazonium species corresponds to **7a** where the ring methylene group C(5) is placed *syn* to the carbonyl group.

Experimental

*3-Bromo-*N*-[(2*S*)-2-methoxymethylpyrrolidin-1-yl]benzamide* (**9**): 2-Bromobenzoic acid was initially converted into its acid chloride ($SOCl_2$, DMF cat., CH_2Cl_2) and then allowed to react under standard conditions with (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) to furnish the 2-bromobenzhydrazide **9**: M.p. 116–117 °C. ^{1}H NMR ($CDCl_3$, δ ppm, *J* Hz): 1.52–1.58 (1H, m), 1.73–1.89 (2H, m), 2.90 (1H, q, *J* 8.5), 3.07–3.22 (1H, m), 3.30 (3H, s), 3.32–3.41 (3H, m), 3.42 (1H, dd, *J* 5.6, 9.7), 3.53 (1H, dd, *J* 5.6, 9.7), 7.12–7.32 (2H, m), 7.39 (1H, dd, *J* 1.8, 7.5), 7.49 (1H, dd, *J* 1.0, 7.9). ^{13}C NMR ($CDCl_3$, δ ppm) 21.4, 26.5, 55.3, 59.2, 64.4, 74.9, 119.6, 127.5, 129.5, 131.3, 133.2, 136.9, 166.5. IR (KBr) 3470, 3201, 1660, 1536, 1317, 1130, 929 cm^{-1}. *m/z* (EI) 314 (M^+,1), 312 (M^+,1), 269 (97), 267 (100), 202 (27), 200 (28), 184 (99), 185 (94).

*3-Hydroxy-2-[(2*S*)-2-methoxymethylpyrrolidin-1-yl]-2,3-dihydro-1*H*-isoindolin-1-one* (**8**): A solution of PhLi (1.22 ml, 1.8 M in cyclohexane/Et_2O, 2.2 mmol) was added dropwise at –78 °C under Ar to a stirred solution of the benzhydrazide **9** (630 mg, 2.0 mmol) in THF (70 ml). After stirring for 20 min at –78 °C, *n*BuLi (1.38 ml, 1.6 M in hexanes, 2.2 mmol) was added dropwise followed by DMF (365 mg, 5.0 mmol). The reaction mixture was stirred at –78 °C for 1 h, then allowed to warm to room temperature over a period of 2 h and finally quenched by addition of saturated aqueous NH_4Cl (20 ml). The mixture was extracted with Et_2O (3 × 50 ml) and the combined organic layers were dried (Na_2SO_4). Evaporation of solvent *in vacuo* left an oily residue which was purified by flash column chromatography on silica gel with acetone-hexanes (30:70) as eluent. Coumpound **8** was obtained as a mixture of diastereomers (85:15), major diastereomer: ^{1}H NMR ($CDCl_3$, δ ppm, *J* Hz): 1.49–1.67 (1H, m), 1.74–1.92 (1H, m), 1.94–2.12 (1H, m), 3.13–2.30 (1H, m), 3.65 (1H, q, *J* 5.3), 3.99–4.13 (1H, m), 5.64 (1H, d, *J* 3.9), 5.79 (1H, d, *J* 3.9), 7.43–7.61 (3H, m), 7.74 (1H, d, *J* 7.6). ^{13}C NMR ($CDCl_3$, δ ppm) 23.0, 26.8, 52.3, 58.6, 60.1, 75.9, 82.0, 122.9, 123.3, 129.4, 131.1, 132.4, 142.7, 165.6. IR (KBr) 3348, 1706, 1468, 1100 cm^{-1}. *m/z* (EI) 263 (M+, 5), 245 (23), 217 (100).

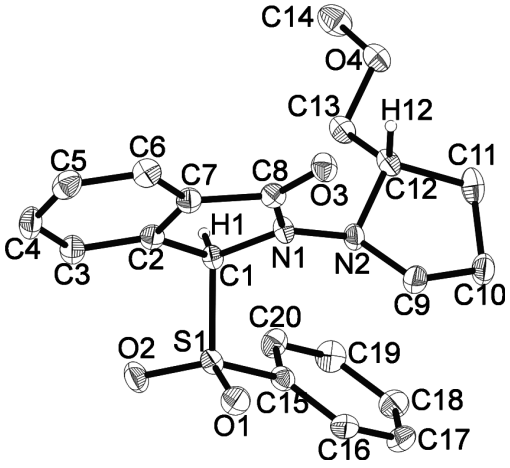


Fig. 3 Crystal structure of (3*S*)-3-benzenesulfonyl-2-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-2,3-dihydro-1*H*-isoindol-1-one (**10**).

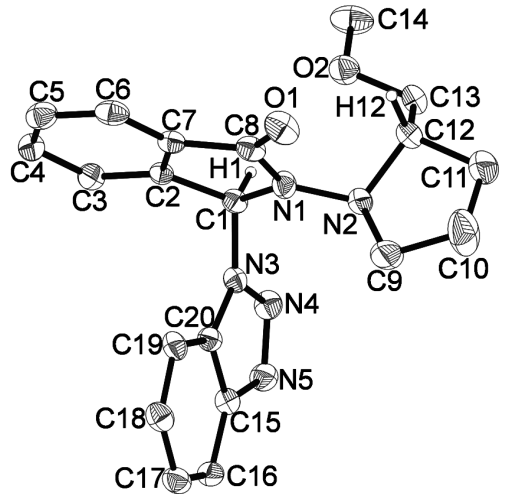


Fig. 4 Crystal structure of (3*S*)-3-(1*H*-benzotriazol-1-yl)-2-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-2,3-dihydro-1*H*-isoindol-1-one (**11**)

General procedure for the preparation of derivatives **10** *and* **11**. A solution of hydroxyphthalimidine **8** (262 mg, 1 mmol), sodium benzenesulfinate (180 mg, 1.1 mmol) or benzotriazole (131 mg, 1.1 mmol) and *p*-toluenesulfonic acid monohydrate (228 mg, 1.2 mmol for **10**; 19 mg, 0.1 mmol for **11**) in toluene (30 ml) was refluxed for 3 h in a Dean-Stark apparatus. The solution was then cooled, washed with saturated $NaHCO_3$ solution (2 × 10 ml) and dried ($MgSO_4$). After evaporation of the solvent, the crude residue was subjected to chromatography on SiO_2 using $CHCl_3$–Et_2O–hexanes (50:20:30) as eluent.

*(3*S*)-3-Benzenesulfonyl-2-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-2,3-dihydro-1*H*-isoindol-1-one*[10] (**10**): M.p. 131–132 °C (hexane–toluene). Anal. Calcd: C, 62.15; H, 5.75; N, 7.25. Found: C, 62.3; H. 5.6, N, 7.3. Crystal data: $C_{20}H_{22}N_2O_4S$, M_r = 386.46, *F*(000) = 816, colourless crystal, orthorhombic system, *a* = 8.7916(15), *b* = 11.811(2), *c* = 18.137(3) Å, V = 1883.3(6) Å^3, Space group $P2_12_12_1$, *Z* = 4, D_c = 1.363 g cm^{-3}, μ(Mo Kα) = 0.201 cm^{-1}.

*(3*S*)-3-(1*H*-benzotriazol-1-yl)-2-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-2,3-dihydro-1*H*-isoindol-1-one*[10] (**11**): M.p. 175–176 °C (hexane–toluene). Anal. Calcd: C, 66.1; H, 5.8; N, 19.3. Found: C, 66.25; H. 6.0, N, 19.4. Crystal data: $C_{20}H_{21}N_5O_2$, M_r = 363.42, *F*(000) = 768, colourless crystal, monoclinic system, *a* = 9.3020(15), *b* = 22.728(4), *c* = 9.5212(16) Å, β = 115.980(2) °, V = 1809.5(5) Å^3, Space group $P2_1$, *Z* = 4, D_c = 1.334 g cm^{-3}, μ(Mo Kα) = 0.090 cm^{-1}. The unit cell contains two crystallographically independent molecules.

The intensity data were collected at 100 K on a Bruker AXS SMART three-circle diffractometer with graphite monochromatised

Mo Kα radiation (λ=0.71073 Å) and equipped with a CCD two-dimensional detector. Collection with ω and φ scans.

The structures were solved by direct methods and expanded using Fourier maps. All non hydrogen atoms were refined anisotropically. Hydrogen atoms positions were refined but their temperature coefficient were fixed to 1.2 times the U_{eq} of the atoms they are bound to. The SHELXTL[10] crystallographic software package was used for all calculations.

For **10**, 4412 independent reflections were used $-11< h <11$, $-15< k <15$, $-23< l < 24$, θ_{max} =28.53 °, R_1 = 0.0306, Rw_2 = 0.0771; the estimated standard deviations for non-hydrogen atoms were in the range 0.0001–0.0003 Å for the bond lengths and 0.07–0.15 ° for the bond angles. Further details of the X-ray structure data are available on request from the Cambridge Crystallographic Data Centre (deposition number CCDC 256032).

For **11**, 7573 independent reflections were used $-11< h <11$, $-30< k <30$, $-12< l <12$, θ_{max} =28.55°, R_1 = 0.0489, Rw_2 = 0.1020; the estimated standard deviations for non-hydrogen atoms were in the range 0.003–0.005 Å for the bond lengths and 0.2–0.3 ° for the bond angles. The two crystallographically independent molecules are related by a pseudo 2_1 axis perpendicular to b. The differences are less than 0.02 Å for the bond length and less than 1.5° for the bond angles. Further details of the X-ray structure data are available on request from the Cambridge Crystallographic Data Centre (deposition number CCDC 256031).

Received 28 December 2004; accepted 17 March 2005
Paper 05/2995

References

1 B. Koenig, U. Leser, W. Schaefer, H. Zilch, T. Poll, H. Leinert and A. Maertens, *Ger. Offen.* DE 4103177 (1992); *Chem. Abstr.*, 1992, **117**, 212489.
2 T. Iino, Y. Sato, T. Nishimura, M. Banba, J. Eiki and T. Nagase, *Jpn. Kokai Tokkyo Koho* JP 2002255967 (2002); *Chem. Abstr.*, 2002, **137**, 232648.
3 (a) J.M. Chen, X. Chen, M. Fardis, H. Jin, C.U. Kim and L.N. Schacherer, *PCT Int. Appl.* 2004035577 (2004); *Chem. Abstr.*, 2004, **140**, 375156; (b) *PCT Int. Appl*. 2004035576 (2004); *Chem. Abstr.*, 2004, **140**, 375155.
4 M.-J. Blanco-Pillado, M.P. Chappell, M. Garcia de la Torre, N. Diaz Buezo, J.E. Fritz, W.G. Holloway, J.E. Matt Jr., C.H. Mitch, C. Pedregal-Tercero, S.J. Quimby, M.G. Siegel, D.R. Smith, R.D. Stucky, K. Takeuchi, E.M. Thomas and C.N. Wolfe, *PCT Int. Appl*. 20040401 (2004); *Chem. Abstr.*, 2004, **140**, 303538.
5 C.A. Demerson and I.L. Jirkovsky, *US Pat.* US 4668687 (1987); *Chem. Abstr.*, 1983, **98**, 160738.
6 J.S. Park, K.U. Kyong, J.Y. Jae, E.S. Yoo, Y.S. Byun and M.H. Park, *Arch. Pharm. Res.*, 2001, **24**, 367.
7 A. Mertens, H. Zilch, B. Koenig, W. Schaefer, T. Poll, W. Kampe, H. Seidel, U. Leser and H. Leinert, *J. Med. Chem.*, 1993, **36**, 2526.
8 H. Suzuki, S. Aoyagi and C. Kibayashi, *J. Org. Chem.*, 1995, **60**, 6114.
9 E. Deniau and D. Enders, *Tetrahedron Lett.*, 2002, **43**, 8055.
10 E. Deniau, D. Enders, A. Couture and P. Grandclaudon, *Tetrahedron: Asymmetry*, 2005, **16**, 875-881.
11 G.M. Sheldrick, *SHELXTL, Program for Crystal Structure Solution and Refinement*, Bruker AXS Inc., Madison, WI, 1997