Pergamon

Tetrahedron Letters 39 (1998) 8081–8084

TETRAHEDRON
LETTERS

Preparation and Diastereoselective Functionalization of a New Chiral Non Racemic Bicyclic Hydrazinolactam

**Fanny Roussi[a], Martine Bonin[a], Angèle Chiaroni[b], Laurent Micouin[a], Claude Riche[b]
and Henri-Philippe Husson[a]***

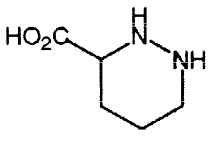
a) Laboratoire de Chimie Thérapeutique associé au CNRS, Faculté des Sciences Pharmaceutiques et Biologiques,
Université René Descartes, 4 Avenue de l'Observatoire, 75270 Paris cedex 06, France.
b) Institut de Chimie des Substances Naturelles, Avenue de la Terrasse, F-91198 Gif-sur-Yvette, France.

Received 26 July 1998; accepted 27 August 1998

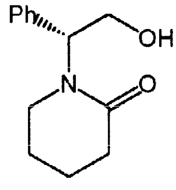
Abstract: : Starting with *R*-(-)-phenylglycinol, the synthesis of a new bicyclic hydrazinolactam 3 was realized on a multigram scale. The reaction scope of the corresponding enolate with various electrophiles has been studied. Good to excellent diastereoselectivities were obtained.

The last ten years have shown an increased interest in the chemistry and in the biological properties of cyclic hydrazine derivatives.[1] Structures like piperazic acid **1** are present in a large number of pharmacologically active molecules that include potent antitumour antibiotics in the matlystatin or luzopeptin series[2] or synthetic products with therapeutic applications, like Cilazapril.[3]

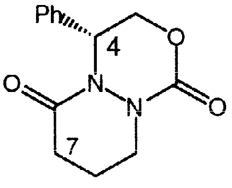
In this area, a correctly functionalized hydrazinolactam core can provide useful new conformationally constrained peptidomimetics.[4] Synthetic strategies for such a pattern must therefore be versatile enough to allow the introduction of various substituents.



1



2



3

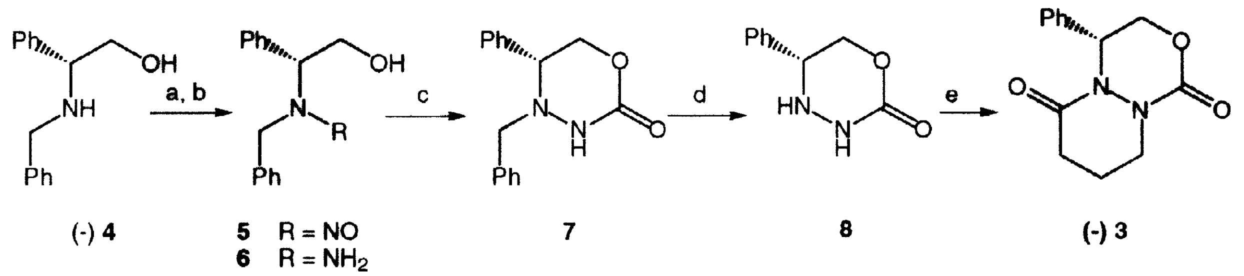
Previous studies in our laboratory toward the asymmetric synthesis of lactam derivatives have provided excellent diastereoselectivities in the alkylation of the homochiral synthon **2** via bicyclic chelated enolate intermediates.[5]

Our ongoing interest in natural and non-natural biologically active compounds prompted us to investigate the new chiral hydrazino-lactam synthon **3** derived from (*R*)-(-)-phenylglycinol. We therefore wish to report a short and efficient route to this novel enantiopure bicyclic hydrazinolactam and the diastereoselective formation of various 7-substituted derivatives.

Our route to **3** is outlined in Scheme 1. The strategy for the construction of such a bicyclic hydrazine involved the regioselective substitution of chiral diazacarbamate **8** with an halocarbonyl compound. This enantiopure precursor could be obtained in four steps from N-benzyl (*R*)-(-)-phenylglycinol **4** on a multigram scale.[6]

Fax: (33) 01 43 29 14 03; e-mail: husson@pharmacie.univ-paris5.fr

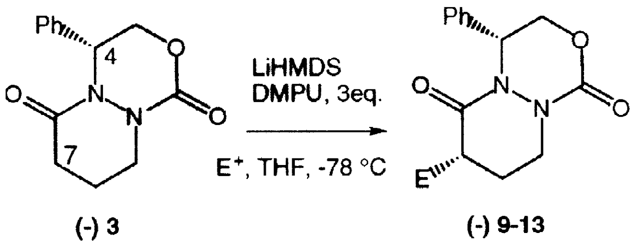
0040-4039/98/$ - see front matter
PII: S0040-4039(98)01813-9



Scheme 1. *Reagents and conditions* : a) $NaNO_2$, H_2O/HCl, 70°C, 92%; b) $LiAlH_4$, Et_2O, -78 °C to -10 °C, 84% ; c) Im_2CO, CH_2Cl_2, r.t., 74%; d) H_2, $Pd(OH)_2$, 10 bars, MeOH, 97%; e) $Br(CH_2)_3COCl$, K_2CO_3, CH_3CN, r.t., 81%.

The reduction of the nitroso-derivative **5** was not straightforward and required a low temperature (-78 °C to -10 °C) in order to obtain hydrazine **6** in good yield. Subsequent treatment with carbonyl diimidazole afforded the cyclic diazacarbamate **7**. Pure **8** was then obtained by N-debenzylation, the use of $Pd(OH)_2$ as a catalyst under pressure of hydrogen proved to be the best conditions for this transformation. Trituration of the crude reaction mixture led to white crystals in 55% overall yield from **4**. Finally, diazacompound **8** was condensed with bromobutyryl chloride under classical basic conditions to give the bicyclic derivative **(-) 3.**[7]

We then turned our attention toward the functionalization of the C-7 position *via* classical enolate chemistry, in the expectation that steric factors would induce good diastereoselectivity. As observed in another related series,[8] the use of strong bases like LDA led to benzylic deprotonation and subsequent β-elimination. After optimization, hexamethylsilylamides appeared to be more convenient for the generation of the enolate, leading to less than 10% of this undesirable elimination. We then investigated the reactivity of such an anion with several electrophiles under various conditions (Table).



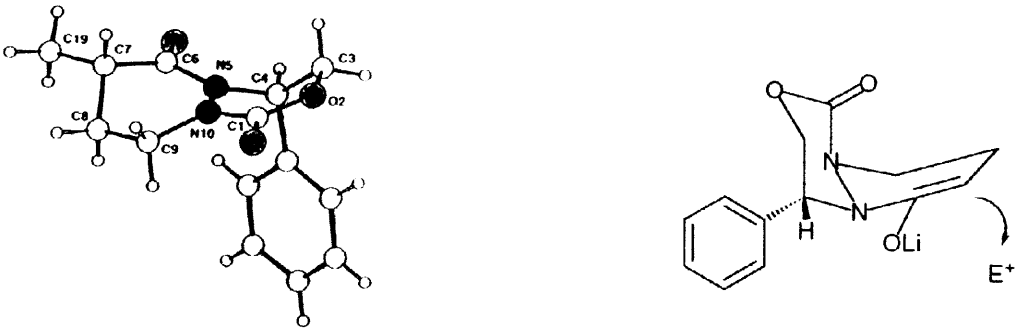
E^+	Compound	Yield[a] %	d.e.[b] %
CH_3I	**9**	57	46
CH_3I	**9**	67	77[c]
$CH_2=CHCH_2Br$	**10**	56	0
$PhCH_2Br$	**11**	63	95
$BrCH_2CO_2tBu$	**12**	50	>95
DBAD	**13**	68	>95

a) Isolated yield.
b) Determined by H^1 NMR of the crude reaction mixture
c) LiCl (3 eq.) was used instead of DMPU.

Table - Enolate Alkylation of (-) **3**, Survey of Electrophiles

In a typical procedure, deprotonation of **3** with 1.1 eq. of LiHMDS and subsequent reaction with halogenated derivatives in the presence of DMPU (3 eq.) afforded alkylation products **9-12** in good yields with up to 95% diastereoselectivity (Table)[9]. In the case of methyl iodide, better results were obtained using LiCl (3 eq.) as an additive (compound **9** : yield, 67% ; d.e., 77%). For allyl bromide, no diastereoselectivity was observed, probably due to an SN_2' mechanism. Reaction with di-*ter*-butylazodicarboxylate[10] as an electrophile gave the hydrazino derivative **13** with good yield and excellent diastereoselectivity. For all the major diastereomers **9**, **11-13**, ^{1}H-NMR spectra proved to be almost identical for the H-3, H-4, H-8 and H-9 signals.

The absolute configuration of the newly created asymmetric center was determined by crystal structure X-ray analysis of the methyl derivative (-) **9** (Figure).[11] It appeared that this original heterocyclic system adopts an essentially planar conformation with the bulky phenyl group in a quasi-axial position and the methyl substituent in a pseudo-equatorial orientation.



X-ray analysis of compound **9**

Origin of diastereoselectivity

Figure

Alkylation is apparently preferred *syn* to the most hindered side of the enolate intermediate. This unexpected diastereoselectivity is probably the result of a partial pyramidalization of the bridghead amide N-atom, converting the original planar bicycle **3** into a strongly folded one (Figure). In such a model, the phenyl group is partially pushed out of the plane, leading to a molecule with a more congested upper side. The electrophile will then approach from the other, less hindered side.

In conclusion, we have developped an efficient asymmetric synthesis of a new diazabicyclic system incorporating two different carbonyl functions. We have shown that in most cases, alkylation occurred with a remarkable diastereoselectivity. A large variety of functionalizations can be efficiently conceived with this new type of diazacompounds. We are currently exploring applications to the preparation of biologically active derivatives.

References and Notes

1. Hale, K. J. ; Cai, J. ; Delissir, V. ; Manaviazar, S. ; Peak, S. A. ; Bhatia, G. S. ; Collins, T. C. ; Jogiya, N. *Tetrahedron* **1996**, *52*, 1047-1068.
2. (a) Greck, C. ; Bischoff, L. ; Genêt, J.-P. *Tetrahedron: Asymmetry* **1995**, *6*, 1989-1994. (b) Tamaki, K. ; Kurihara, S. ; Oikawa, T. ; Tansawa, K. ; Sugimura, Y. *J. Antibiot.* **1993**, *47*, 1481-1492.
3. Attwood, M. R. ; Hassall C. H. ; Kröhn, A. ; Lawton, G., Redshaw, S. *J. Chem. Soc., Perkin Trans. I* **1986**, 1011-1019.
4. Hanessian, S. ; Mc Naughton-Smith, G. ; Lombart, H.-G. ; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789-12854.

5. (a) Micouin, L. ; Varea, T. ; Riche, C. ; Chiaroni, A. ; Quirion, J.-C. ; Husson, H.-P. *Tetrahedron Lett.* **1994**, *35*, 2529-2532. (b) Micouin, L. ; Jullian, V. ; Quirion, J.-C. ; Husson, H.-P. *Tetrahedron: Asymmetry* **1996**, *7*, 2839-2846.
6. N-benzyl hydrazine **6** was synthesized at 100g scale in the "Service de Synthèse et de Développement" Laboratory, Besselièvre, R.; Biron, J.-P. ; ICSN-CNRS, Gif-sur-Yvette.
7. All new compounds showed satisfactory NMR spectroscopic data, together with elemental and/or mass spectrometry data. Compound (-) **3** : $[\alpha]_D$ = - 210 ($CHCl_3$, c = 0.95); ^1H NMR (300 MHz; $CDCl_3$), (δ, ppm; J, Hz) : 1.92 (dt, 1H, J = 12.4, 6.2, H-9), 2.18 (m, 1H, H-9), 2.55 (dt, 1H, J = 17.3, 6.6, H-8), 2.65 (ddd, 1H, J = 17.3, 7.7, 6.3, H-8), 3.24 (ddd, 1H, J = 13.0, 5.5, 5.2, H-10ax), 4,33 (dt, 1H, J = 13.0, 6.3, H-10eq) 4.65 (dd, 1H, J = 11.4, 4.2, H-4), 4.60 (dd, 1H, J = 11.4, 4.9, H-4), 5.96 (br. t, 1H, J = 4.5, H-5), 7.30 (m, 5H, Ph); ^{13}C NMR (δ, ppm; 75.43 MHz, $CDCl_3$) : 20.0 (C-8), 27.1 (C-7), 43.7 (C-9), 50.8 (C-4), 69.0 (C-3), 126.5-129.1 (CH-Ar.), 134.8 (Cq-Ar.), 150.0 (C-1), 167.5 (C-6); IR (neat) : 3054, 2986, 1720-1680 cm^{-1}; MS (CI) : 247 (MH^+); Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C 63.40, H 5.73, N 11.38; Found : C 63.39, H 5.61, H 11.38.
8. (a) Ragan, J. A. ; Claffey, M. C. *Heter.* **1995**, *41*, 57-70. (b) Meyers, A. I. ; Kunnen, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 4405-4407.
9. To a solution of pyridazinolactam **3** (160 mg, 0.65 mmol) and DMPU (235 µL, 1.95 mmol) in dry THF (3 mL) cooled to -78 °C was added, under argon, 715 µL of a 1.0 M solution of LiHMDS. The reaction mixture was stirred for 0.5 h at -78 °C, and benzyl bromide (235 µL, 1.95 mmol) was added. The mixture was stirred for 3 h at -78 °C and quenched with 5 mL of a buffer solution (pH 5.8). The aq. layer was extracted three times with ethyl acetate (15 mL) and the combined organic layers were dried over $MgSO_4$. Removal of the solvant and purification of the residue by flash chromatography on silica gel (eluent : ethyl acetate/cyclohexane 3/7) gave 132 mg (61 % yield) of **11** as a white crystalline solid. Diastereomeric excess = 95%. $[\alpha]_D^{25}$ = - 114 (c = 1.65, $CHCl_3$). ^1H NMR data for the major diastereomer (300 MHz, $CDCl_3$) (δ, ppm; J, Hz) : 1.58 (m, 1H, H-8), 2.12 (dt, 1H, J = 4.3, 9.1, H-8), 2.65 (d, 1H, J = 9.4, CH_2Ph), 2.73 (m, 1H, H-7), 3.22 (ddd, 1H, J = 12.4, 8.6, 3.6, H-9eq.), 3.38 (d, 1H, J = 9.4, CH_2Ph), 4.06 (dt, 1H, J = 12.4, 8.6, H-9ax.), 4.58 (dd, 1H, J = 11.4, 4.7, H-3), 4.71 (dd, 1H, J = 11.4, 2.9, H-3), 5.98 (br. t, 1H, J = 4.1, H-4), 7.34 (m, 10 H, Ar.). ^{13}C NMR (75.43 MHz, $CDCl_3$; δ, ppm) : 24.9 (C-8), 35.5 (CH_2Ph), 41.2 (C-7), 43.3 (C-9), 49.9 (C-4), 69.2 (C-3), 126.5-129.1 (CH-Ar.), 134.6, 138.6 (Cq-Ar.), 149.5 (C-1), 171.0 (C-6). IR : 1684 cm^{-1}. MS (CI) : 337 $[MH]^+$. Anal. Calcd. for $C_{20}H_{20}N_2O_3$ + 1/3 H_2O : C 70.01, H 6.31, N 8.26. Found: C 70.16, H 6.08, N 8.18.
10. Evans, D. A. ; Britton, T. C. ; Dorow, R. L. ; Dellaria, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6395-6397.
11. Compound (-) **9**, Mp : 111°C, colourless crystal (hexane/ethyl acetate); $C_{14}H_{16}N_2O_3$, Mw = 260.29, monocyclic system, space group C 2, Z = 4, a = 25.828 (15), b = 5.540 (3), c = 9.787 (6) Å, β = 110.90 (3) °, V = 1308.3 $Å^3$, d_c = 1.322 g cm^{-3}, F(000) = 552, λ (Cu Kα) = 1.5418 Å, μ = 0.77 mm^{-1}; 1533 data measured (Nonius CAD-4 diffractometer), 1401 unique (Rint = 0.036) of which 1046 considered as observed with $I \geq 2.0\ \sigma(I)$; absorption ignored. The structure was solved by *SHELXS86* and refined by *SHELXL93*. Refinement converged to R_1 (F) = 0.0557, for 1046 Fo with Fo $\geq 4\ \sigma$(Fo) and $wR_2(F^2)$ = 0.1618 (for all the 1401 data with goodness-of-fit S = 1.153). Lists of the fractional atomic coordinates, thermal parameters, distances, bond and torsion angles have been deposited at the Cambridge Crystallographic Data Centre, U.K., as Supplementary Material (CIF file).