

**SYNTHESIS AND STRUCTURAL ASSIGNMENT OF FUNCTIONALIZED
8,9-DIAZATRICYCLO[4.4.0.0^{1,5}]DECANE: A NEW TRICYCLIC SYSTEM
INCLUDING THE PYRIDAZINE RING**

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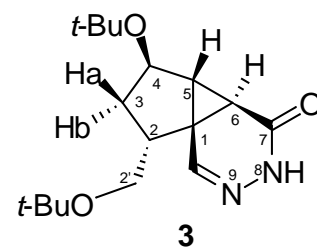
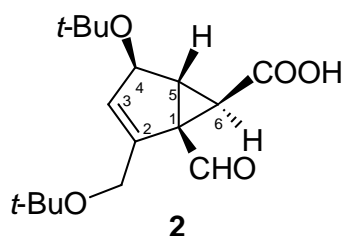
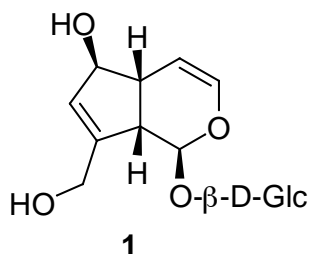
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Abstract - Reaction of hydrazine hydrate with the dipivaloyl ester of (1*S*,
4*R*, 5*R*, 6*R*)-4-hydroxy-2-hydroxymethyl-1-formylbicyclo[3.1.0]hex-2-ene-
6-carboxylic acid (**2**) afforded (1*S*, 2*R*, 4*R*, 5*R*, 6*R*)-8,9-diaza-2-[(2,2-
dimethylpropanoyloxy)methyl]-7-oxotricyclo[4.4.0.0^{1,5}]dec-9-en-4-yl 2,2-
dimethylpropanoate (**3**). The structure and conformation of the new 8,9-
diazatricyclo[4.4.0.0^{1,5}]dec-9-ene system were determined by X-Ray
cristallography and 2D NMR experiments.

There is currently an increasing interest for the use of iridoid glycosides as chiral natural precursors of cyclopentanoid compounds of biological interest. Indeed, apart from their classical use in prostaglandin synthesis,¹⁻⁶ iridoids were more recently employed as starting material for the preparation of various carbocyclic nucleoside analogues⁷⁻⁹ and insect antifeedants.¹⁰ In this respect, aucubin (**1**), readily available in large amounts from the fresh fruits and leaves of *Aucuba japonica* Thunb. (Cornaceae),¹¹ appears as particularly suitable for the development of new chiral synthons. For our part, we recently reported the conversion of aucubin into conformationally restricted cyclopropane-fused analogues of manostatins, through the intermediacy of the pivaloyl diester of (1*S*, 4*R*, 5*R*, 6*R*)-4-hydroxy-2-hydroxymethyl-1-formyl-

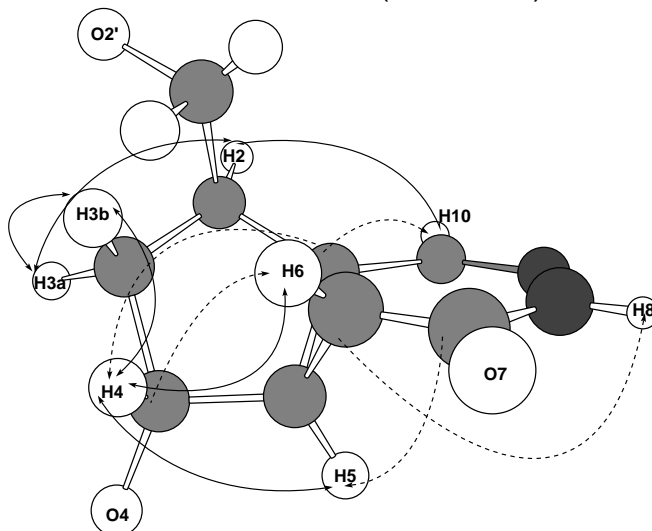
bicyclo[3.1.0]hex-2-ene-6-carboxylic acid (**2**).¹² A major interest of **2** lies in the difference in the oxidation levels of the formyl and carboxylic acid groups, which both arise from a masked formyl function present in aucubin aglycone.



In a continuation of our work, we were interested in the use of **2** for the synthesis of functionalized fused heterocycles. We describe herein a facile entry to the 8,9-diazatricyclo[4.4.0.0^{1,5}]decane series, exemplified by compound (**3**), together with a NMR and X-Ray structure analysis of this novel tricyclic system.

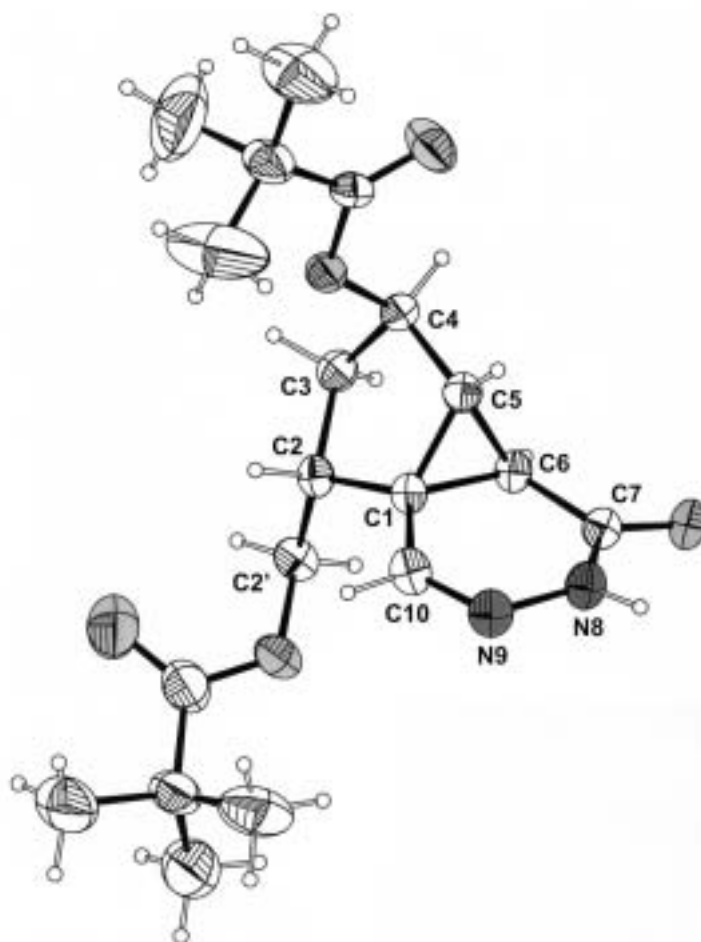
Obtainment of target tricyclic derivative (**3**) from **2** should involve: (i) construction of a new fused 4,5-dihydro-3(2*H*)-pyridazine ring, (ii) reduction of the cyclopentene double bond. The conversion of γ -amino acids into pyridazinones and phthalazinones by the use of hydrazine hydrate is well documented.¹³ In our case, the reducing properties of this reagent¹⁴ led us to envisage the possibility of the simultaneous reduction of the cyclopentene double-bond. Indeed, thermal decomposition of hydrazine affords diimide, a reducing species which reduces double bonds through a six-membered transition state.¹⁴ As expected, treatment of **2** with excess hydrazine hydrate readily afforded **3**, as a single reaction product, in one step and 60% overall yield.

Configuration of the new chiral center at C-2 was deduced as (2*R*) from NOESY correlations observed between H-C2 and H-C10 and Ha-C3 (Scheme 1).



Scheme 1: Selected ¹H-¹H NOESY (plain arrows) and ¹³C-¹H COLOC (dashed arrows) correlations. Pivalic ester groups were omitted for clarity

It was further confirmed by X-Ray diffraction analysis. The diastereoselectivity observed for the cyclopentene reduction should be emphasized. Indeed, hydrogen transfer exclusively occurred by the less hindered ("exo") face of the bicyclo[3.1.0]hexene system. X-Ray structure analysis of **3** (Scheme 2) clearly established the configurations at C-6, C-5, and C-2, deduced from the known (*R*) configuration at C-4, and permitted in addition to determine the conformation of the molecule.



Scheme 2 : Ortep drawing of the molecule. Displacement ellipsoids are shown at the 30% probability level.

Torsion angles show that the pyridazone ring is nearly planar, with the cyclopropane atom C-5 above the mean plane of that ring by 1.263 (3) Å. The cyclopentane ring exhibits an envelope conformation with atom C-3 deviated out of the mean plane of the other four atoms by - 0.490 (4) Å. The dihedral angles between the cyclopropane ring and the mean planes of the pyridazone and cyclopentane rings are 106.7 and 101.3°, respectively. Analysis of the correlations observed on the NOESY spectrum (Scheme 1) indicates that the cyclopropane and cyclopentene rings adopt a similar conformation in solution.

Purely lactam form, with protonation at N-8, of the pyridazone ring was established from both X-

Ray analysis and strong ^1H - ^{13}C correlations observed on the COLOC spectrum of **3**, between C-7 and H-5 on one hand, and C-6 and N-H on the other hand. The lactam tautomeric form observed here in the presence of a fused cyclopropane was previously described in various other heterocycles, including pyridazinones, pyridinones, and phthalizinones.^{13, 15, 16}

In summary, compound (**3**) containing the new 8,9-diazatricyclo[4.4.0.0^{1,5}]decane skeleton was satisfactorily obtained in one step from **2**, which can be prepared on a multi-gram scale from aucubin.¹² The major interest of **3** lies in its overall extremely strained structure induced by the fused cyclopropane ring. Indeed, **3** should be considered as a new scaffold possessing three sites suitable for chemical diversification in a given geometry. Presence of the fused pyridazine and cyclopropane rings also lead to consider **3** as an interesting precursor toward 3,4-diazanorcaradienes, thus giving an entry to other new heterocycles.^{17, 18}

EXPERIMENTAL

General. Column chromatography : flash silica-gel 60 Merck (35-70 μm). mp : Leica melting point microscope ; uncorrected. Optical rotation : c in g/100 mL ; Perkin-Elmer 241 Polarimeter. IR spectrum : in cm^{-1} ; Nicolet 510 FT-IR spectrometer. NMR spectra : Bruker AC 300 at 300 (^1H) and 75 MHz (^{13}C) ; δ in ppm rel. to solvent peak as internal standard ($\delta(\text{CDCl}_3)$ 7.27), J in Hz ; assignments by NOESY experiment, C,H shift-correlation spectra (HETCOR and COLOC) and DEPT135 experiment. MS : in m/z ; Nermag R10-10C (DCI-MS with NH_3 as reagent gas). Elemental analysis was performed at the I.C.S.N. (CNRS, Gif-sur-Yvette, France).

(1S, 2R, 4R, 5R, 6R)-8,9-Diaza-2-[(2,2-dimethylpropanoyloxy)methyl]-7-oxotricyclo[4.4.0.0^{1,5}]dec-9-en-4-yl 2,2-dimethylpropanoate (**3**): To a solution of **2** (300 mg, 0.82 mmol) in 95% EtOH (8 mL), 200 μL of 98% hydrazine monohydrate (4.09 mmol) was added at rt. The mixture was refluxed for 15 h and the solvent was evaporated under reduced pressure. The residue was taken up in CH_2Cl_2 (30 mL), the solution was washed with water (2 \times 20 mL), brine (20 mL), dried over MgSO_4 , and evaporated. The crude residue was chromatographed on silica gel (cyclohexane/AcOEt/AcOH 7/3/0.1) to afford **3** as a white solid (178 mg, 60%), recrystallized from n-hexane as colorless needles: mp 163 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{20} = +27.3^\circ$ ($c = 1.1$, CH_2Cl_2); IR (KBr): 3216 (ν 'NH), 3101(ν 'C-H cyclopropane), 2964, 2934, 2911(ν 'C-H aliphatics), 1732(ν 'CO pivaloates), 1672(ν 'CN and CO amide), 1635, 1481, 1459, 1398, 1364, 1295, 1282, 1173, 1152, 958; ^1H NMR (CDCl_3) δ 8.32 (br s, 1H, exchange with D_2O , H8), 7.30 (s, 1H, H10), 5.37 (d, $J_{4-3b} = 5$, 1H,

H4), 4.21 (dd, $^2J = 11.5$, $J_{2'a-2} = 5$, 1H, H2'a), 3.84 (dd, $^2J = 11.5$, $J_{2'b-2} = 8.5$, 1H, H2'b), 3.14 (dddd, $J_{2-3b} = 11$, $J_{2-2'b} = 8.5$, $J_{2-3a} = 8$, $J_{2-2'a} = 5$, 1H, H2), 2.08 (m, 1H, H6), 1.94 (dd, $^2J = 15.5$, $J_{3a-2} = 8$, 1H, H3a), 1.82 (br d, $J_{6-5} = 2.5$, 1H, H5), 1.28 (ddd, $^2J = 15.5$, $J_{3b-2} = 11$, $J_{3b-4} = 5$, 1H, H3b), 1.22 (br s, 18H, Piv); ^{13}C NMR (CDCl_3) δ 178.1 (Me_3CCO), 164.0 (C7), 142.9 (C10), 74.3 (C4), 64.6 (C2'), 39.3 (C2), 38.7 (Me_3CCO), 38.2 (C1), 30.6 (C3), 29.9 (C75), 27.2, 27.0 (Me_3CCO), 25.4 (C6); DCI-MS: 365 ($[\text{M}+\text{H}]^+$), 382 ($[\text{M}+\text{NH}_4]^+$); Anal. Calcd for $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_5$: C, 62.60; H, 7.75; N, 7.68. Found: C, 62.21; H, 7.66; N, 7.52.

Crystallographic analysis. Colorless crystal of 0.25 x 0.25 x 0.60 mm, crystallized from hexane. $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_5$, $M_w = 364.43$, Monoclinic system, space group $P 2_1$, $Z = 2$, $a = 10.758$ (7), $b = 7.227$ (7), $c = 14.838$ (10) Å, $\beta = 110.67$ (3)°, $V = 1079$ Å³, $d_c = 1.121$ g cm⁻³, $F(000) = 392$, $\lambda(\text{Mo K}\alpha) = 0.71073$ Å, $\mu = 0.081$ mm⁻¹. Data were measured with a Nonius Kappa-CCD area-detector diffractometer, using graphite monochromated Mo K α radiation, in phi scans, up to $\theta = 30.4^\circ$. So, a full sphere of 5753 data was collected ($-10 \leq h \leq 12$, $-9 \leq k \leq 8$, $-21 \leq l \leq 19$) leading to 3280 unique reflections, of which 2754 were considered as observed having $I \geq 2$ sigma (I).^{19,20} The structure was solved by direct methods using program *SHELXS86*²¹ and refined by full-matrix least-squares, based upon unique F^2 with program *SHELXL93*.²² The hydrogen atoms located in difference Fourier maps were fitted at theoretical positions or treated as riding, and assigned an isotropic displacement parameter equivalent to 1.2 that one of the bonded atom. Thus, refinement of 242 parameters converged to $R_1(F) = 0.0606$ for the 2926 observed reflections and $wR_2(F^2) = 0.1688$ for all the 3437 data with a goodness-of-fit S factor of 1.069. The residual electron density was found between -0.18 and 0.41 eÅ⁻³. In the crystal packing, only van der Waals contacts are observed. Full crystallographic results have been deposited as Supplementary Material (CIF file), at the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield road, Cambridge CB2 1EWUK, U. K. (deposition number CCDC 177529).

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