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# Cyclisation of (*R*)- and (*S*)-*N*-Allyl-*N*-(1-phenylethyl) Methoxycarbonylacetamide Mediated by Mn(III): Preparation and Structural Assignment of 3-Aza-2-oxobicyclo[3.1.0]hexanes

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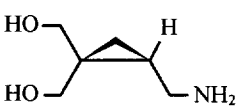
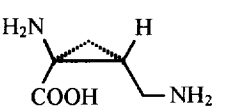
**Abstract:** (*R*)- and (*S*)-*N*-allyl-*N*-(1-phenylethyl)methoxycarbonylacetamide, **5** and **6**, underwent oxidative cyclisation mediated by Mn(III), to give easily separable diastereomeric mixtures of 3-aza-2-oxobicyclo[3.1.0]hexanes **8a,b** and **9a,b**, respectively, whose structures were assigned on the basis of $^1$H NMR spectra and then confirmed by X-ray diffraction analysis of the derivatives **11b** and **14**.


During our studies aimed at the total synthesis of non proteinogenic amino acids which display biological activity, we investigated the oxidative cyclisation of (*S*)-*N*-(2-alken-1-yl)-*N*-(1-phenylethyl)-methoxycarbonylacetamides and acetylacetamides mediated by Mn(III), which proceeds with moderate diastereoselection to give substituted pyrrolidin-2-ones in high enantiomeric purity after chromatographic separation. [1] We wish to report here the cyclisation of (*R*)- and (*S*)-*N*-allyl-*N*-(1-phenylethyl)-methoxycarbonylacetamides mediated by Mn(III), which allows a convenient route to 1-substituted 3-aza-2-oxobicyclo[3.1.0]hexane ring system. [2] This heterocyclic system could be an appropriate starting material for the preparation of compounds containing the cyclopropane moiety, such as aminoalcohols components of antiviral nucleosides, **1**, [3] and conformationally restricted amino acids, **2**. [4] Moreover the 3-azabicyclo[3.1.0] hexane [5] is found in several biologically active natural product frameworks, such as CC-1065 and the duocarmycins [6] and is also potentially convertible to a variety of other nitrogen-containing polycyclic assemblies.



**1**

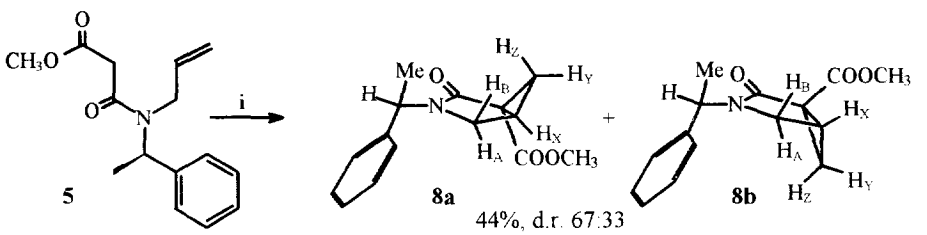


**2**

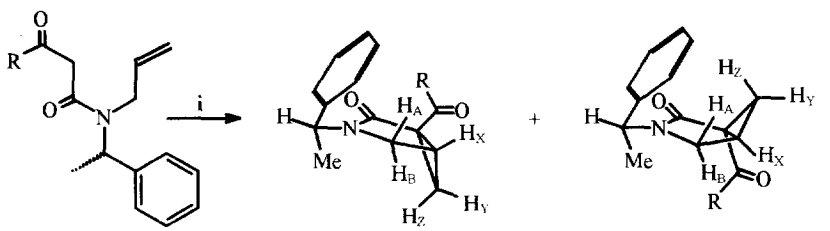
Thus, both (*R*)- and (*S*)-*N*-allyl-*N*-(1-phenylethyl)-methoxycarbonylacetamides, **5** and **6**, were prepared [1] by reaction of methyl malonyl chloride with (*R*)- and (*S*)-*N*-allyl-*N*-(1-phenylethyl)amine, **3** and **4**, respectively. [7] On the

other hand, (*S*)-*N*-allyl-*N*-(1-phenylethyl)-acetylacetamide 7 was obtained by refluxing the amine **4** with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one in toluene. [1] The amides **5** - **7** underwent cyclization by treatment with 2 equiv of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv of $Cu(OAc)_2 \cdot H_2O$ in acetic acid at room temperature. [1] From the reaction 1-substituted 3-aza-2-oxobicyclo[3.1.0]hexanes **8** - **10** were obtained [8] as colorless oils in moderate yield and 2:1 diastereomeric ratio, as determined by g.l.c. of the crude reaction mixture. [9] After separation by flash chromatography, the pure diastereomers **8a,b** and **9a,b** were fully characterised on the basis of their $^1H$ and $^{13}C$ NMR spectra. On the contrary, any attempt to obtain pure isolated **10a** and **10b** failed, although each diastereomer gave well separated sets of signals in both $^1H$ and $^{13}C$ NMR spectra.

The configuration of the diastereomers **8** - **10** could be assigned on the basis of chemical shifts and coupling constants observed in the $^1H$ NMR spectrum [10] and molecular mechanics calculations performed by using MM+ force field. [11] The minimum energy conformation for each diastereomer was calculated and is reported in Schemes 1 and 2. Owing to the shielding effect of the phenyl and cyclopropyl group, in diastereomers **8a** - **10a** $H_A$ and $H_B$ show similar chemical shifts. On the other hand, in diastereomers **8b** - **10b** $H_A$ experiences two shielding effects with respect to $H_B$, thus resulting more shielded than $H_B$.




**Scheme 1.** ***Reagents and conditions:*** **i.** $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OAc)_2 \cdot H_2O$, AcOH, r.t., 12 h.




R = $CH_3O$, **6** R = $CH_3O$, **9a** and **9b**, 42%, d.r. 67:33

R = $CH_3$, **7** R = $CH_3$, **10a** and **10b**, 47%, d.r. 68:32

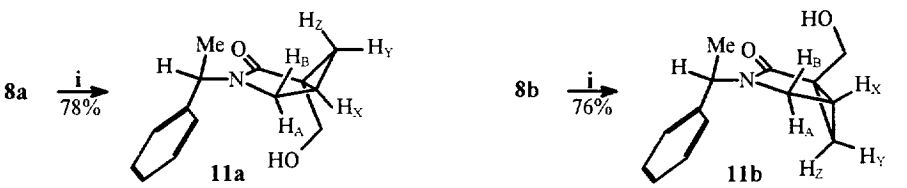
**Scheme 2.** ***Reagents and conditions:*** **i.** $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OAc)_2 \cdot H_2O$, AcOH, r.t., 12 h.

The configurational assignment was also confirmed by the coupling constant values. In fact for diastereomers **8a** - **10a** only $J_{AB}$ was observed for $H_B$, in agreement with the dihedral angle $H_B$-C(4)-C(5)-$H_X$ value which resulted

to be 87.6° from molecular mechanics calculations. In analogy with this result, for diastereomers **8b - 10b** only $J_{AB}$ was observed for $H_A$, in agreement with the calculated value of the dihedral angle $H_A$-C(4)-C(5)-$H_X$.

The configuration was eventually established by X-ray analysis of two derivatives of **8b** and **9b**. In fact, since 1-substituted 3-aza-2-oxobicyclo[3.1.0]hexanes **8** and **9** can be useful intermediates for the preparation of biologically active compounds in the enantiomerically pure form, such as **1** and **2**, some reactions were carried out in order to ascertain their versatility.

First, both diastereomers **8a** and **8b** were treated with $LiBH_4$ in THF at -15 °C, to give the corresponding alcohols **11a** and **11b** in good yield. Whereas **11a** was an amorphous solid, **11b** gave white prisms suitable for X-ray analysis which confirmed the structural assignment of **11a** and **11b** (Figures 2 and 3).




**Scheme 3.** ***Reagents and conditions:*** **i.** $LiBH_4$, THF, -15 °C.

Moreover, an interesting feature was observed in the $^1$H NMR spectra of compounds **11a** and **11b**. In fact the Δν of the ABq of the hydroxymethyl group increases on increasing the concentration, as reported in Figure 1. [12]

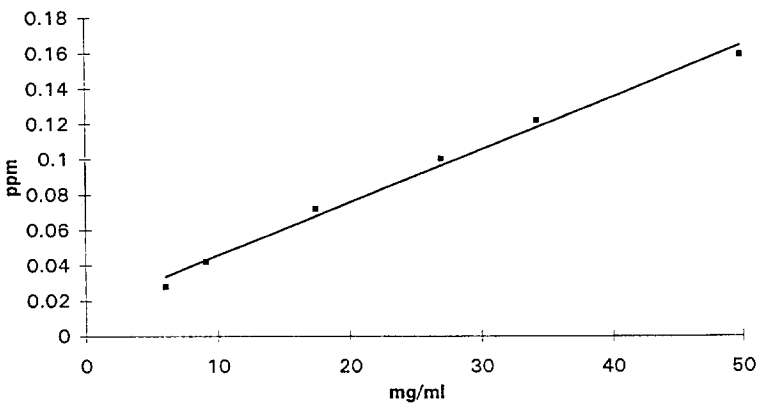



**Figure 1.** The Δν of the ABq of **11a** and **11b** as a function of concentration.

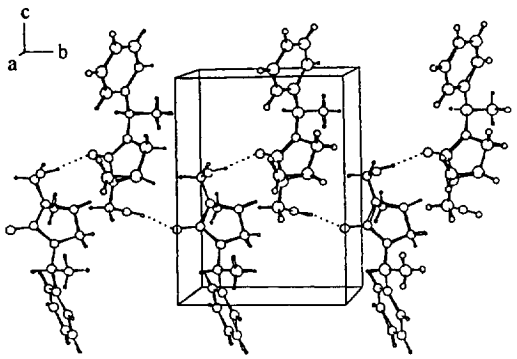
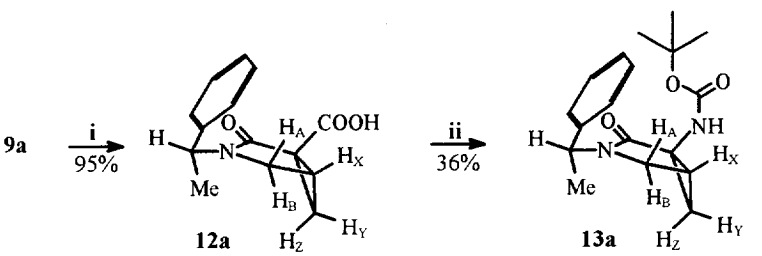


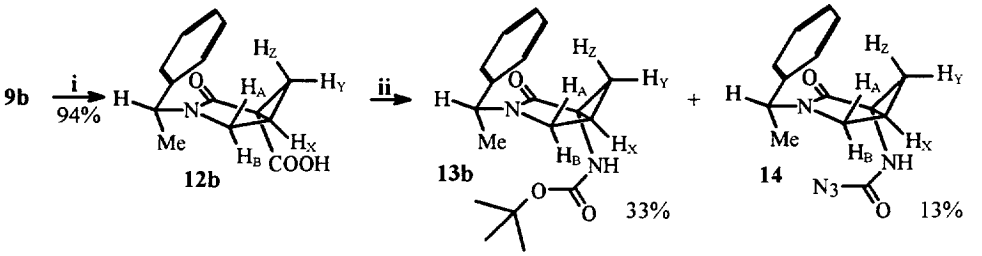

**Figure 2.** Crystal packing of compound **11b**.

This behaviour could be explained by assuming that even at very low concentrations intramolecular hydrogen bonding occurs in very little extent, in agreement with the molecular mechanics calculations performed by using either AMBER [13] and MM+ [14] force fields. In fact in the minimum energy conformation of **11a** and **11b,** the distance between the hydrogen and the oxygen resulted slightly longer (by 0.3 A) than the optimal distance for hydrogen bonding. On the other hand, on increasing the concentration, intermolecular H-bonding takes place leading to an increased diversity between the hydrogens of the hydroxymethyl group and, of course, to an increased $\Delta\nu$ of the ABq. [15] The crystal packing of **11b** determined by X-ray diffraction analysis (Figure 2), represents the maximum of H-bonding, with all the molecules bonded to each other.

Furthermore, in order to obtain intermediates which could lead to conformationally restricted amino acids, such **2**, both **9a** and **9b** were first converted into the corresponding carboxylic acids **12a** and **12b**. By subsequent treatment with diphenylphosphoryl azide in *t*-BuOH, [16] the corresponding carbamates **13a** and **13b** were recovered in moderate yield as clear oils.




**Scheme 4.** ***Reagents and conditions:*** **i.** 2M NaOH. **ii.** $(PhO)_2P(O)N_3$, $Et_3N$, refluxing *t*-BuOH.




**Scheme 5.** ***Reagents and conditions:*** **i.** 2M NaOH. **ii.** $(PhO)_2P(O)N_3$, $Et_3N$, refluxing *t*-BuOH.

However, starting from **9b**, together with **13b** a little amount of the azido carbamate **14** was obtained as a solid which gave crystals suitable for X-ray diffraction analysis (Figure 4), thus confirming the structural assignment to **9a** and **9b**.

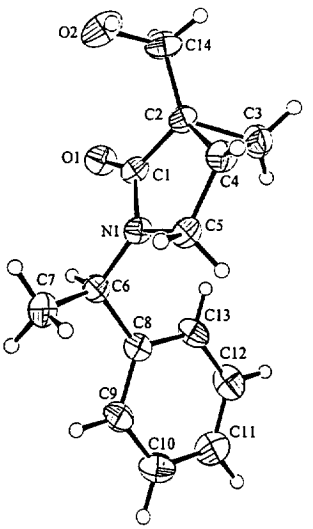



**Figure 3.** ORTEP drawing of **11b.**

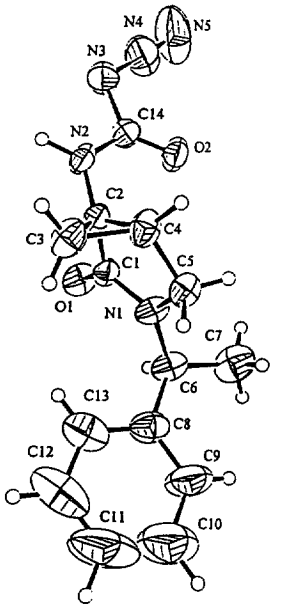



**Figure 4.** ORTEP drawing of **14.**

In conclusion, a new approach to enantiomerically pure 1-substituted-3-aza-2-oxobicyclo[3.1.0]hexanes **8** - **10** was devised, and applications to the total synthesis of biologically active compounds such as **1** and **2** will be reported in due course.

## EXPERIMENTAL

**General Methods**. Melting points were measured on a Electrothermal IA 9000 apparatus and are uncorrected. Ir spectra were recorded on a Nicolet Fourier Transform Infrared 20-SX spectrophotometer. Diastereomeric ratios were determined by GC analysis using a Chrompack 9001 instrument equipped with a Chrompack 7720 capillary column (50 m x 0.25 mm i.d.; stationary phase CP-Sil-5 CB). $^1$H and $^{13}$C NMR spectra were recorded at 200 MHz and 50 MHz, respectively, on a Varian Gemini 200 spectrometer, using $CDCl_3$ as a solvent. Chemical shifts ($\delta$) are reported in ppm relative to TMS and coupling constants (J) in Hz. Assignments were aided by decoupling and homonuclear two-dimensional experiments. Specific rotations were measured on a Perkin Elmer 241 polarimeter. GC-MS analyses were performed with a Hewlett-Packard spectrometer 5890, series II, using a HP-5 capillary column (30 m x 0.25 mm i.d.; stationary phase 5% phenyl methyl silicone). Flash chromatography was performed with silica gel 60 (230-400 mesh). The solvents were distilled under argon before use. $Mn(OAc)_3{\cdot}2H_2O$, $Cu(OAc)_2{\cdot}H_2O$, (*R*)- and (*S*)-1-phenylethylamine and $LiBH_4$ (2M solution in THF) were purchased from Aldrich.

**(*R*)-*N*-Allyl-*N*-(1-phenylethyl)amine (3).** The title compound was prepared in 75% yield as a colorless oil following the literature method [1,7] starting from allyl bromide and (*R*)-1-phenylethylamine. IR ($CDCl_3$): 3348, 925 cm$^{-1}$; $^1$H NMR: 1.38 (d, 3H, J = 6.5), 1.55 (br s, 1H, NH), 3.12 (d, 2H, J = 6.1), 3.82 (q, 1H, J = 6.5), 5.02 - 5.21 (m, 2H), 5.81 - 6.01 (m, 1H), 7.31 (m, 5 ArH); $^{13}$C NMR: 24.7, 50.7, 58.0, 116.2, 127.1, 127.4, 128.9, 137.4, 145.9; $[\alpha]_D$ 63.0 (c 1, $CHCl_3$); GC-MS (EI, 70 eV): *m/z* 161 ($M^+$), 146, 105, 91, 77. Anal. Calcd for $C_{11}H_{15}N$: C, 81.94, H, 9.38; N, 8.69. Found: C, 81.91; H, 9.34; N, 8.66.

**(*S*)-*N*-Allyl-*N*-(1-phenylethyl)amine (4).** The title compound was prepared in 76% yield as a colorless oil following the literature method [1,7] starting from allyl bromide and (*S*)-1-phenylethylamine. $[\alpha]_D$ -63.8 (c 1, $CHCl_3$). Anal. Calcd for $C_{11}H_{15}N$: C, 81.94, H, 9.38; N, 8.69. Found: C, 81.89; H, 9.33; N, 8.62.

**(*R*)-*N*-Allyl-*N*-(1-phenylethyl)methoxycarbonylacetamide (5).** The title compound was prepared in 77% yield as a colorless oil following the literature method [1] starting from (*R*)-*N*-allyl-*N*-(1-phenylethyl)amine **3** and methyl malonyl chloride. IR ($CHCl_3$): 1732, 1625, 930 cm$^{-1}$; $^1$H NMR: 1.51 (d, 3H, 80%, J = 6.5), 1.62 (d, 3H, 20%, J = 6.5), 3.37 - 3.78 (m, 4H), 3.74 (s, 3H), 4.94 - 5.14 (m, 2H + q, 1H, 20%, J = 6.5), 5.45 - 5.86 (m, 1H), 6.08 (q, 1H, 80%, J = 6.5), 7.31 (m, 5 ArH); $^{13}$C NMR: 17.0 (80%), 19.2 (20%), 41.9 (80%), 42.1 (20%), 46.2 (20%), 46.8 (80%), 51.9, 52.8 (80%), 56.9 (20%), 116.8 (20%), 117.3 (80%), 128.0, 128.3, 128.9, 134.7 (20%), 135.0 (80%), 140.8, 167.4, 168.8; $[\alpha]_D$ 171.9 (c 1, $CHCl_3$); GC-MS (EI, 70 eV): *m/z* 261 ($M^+$), 246, 220, 200, 188, 146, 120, 105, 91, 77. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.89; H, 7.30; N, 5.33.

**(*S*)-*N*-Allyl-*N*-(1-phenylethyl)methoxycarbonylacetamide (6).** The title compound was prepared in 75% yield as a colorless oil following the literature method [1] starting from (*S*)-*N*-allyl-*N*-(1-phenylethyl)amine **4** and methyl

malonyl chloride. $[\alpha]_D$ -171.4 (c 1, $CHCl_3$). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.87; H, 7.31; N, 5.31.

**(*S*)-*N*-Allyl-*N*-(1-phenylethyl)-3-oxobutanamide (7).** The title compound was prepared in 71% yield as a colorless oil following the literature method [1] starting from (*S*)-*N*-allyl-*N*-(1-phenylethyl)amine **4** and 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one: IR ($CHCl_3$): 1721, 1650, 930 $cm^{-1}$; $^1H$ NMR: 1.53 (d, 3H, 70%, J = 6.6), 1.63 (d, 3H, 30%, J = 6.6), 1.95 (s, 3H, 70%), 2.30 (s, 3H, 30%), 3.42 - 3.78 (m, 4H), 4.95 - 5.20 (m, 2H + q, 1H, 30%, J = 6.6), 5.45 - 5.91 (m, 1H), 6.08 (q, 1H, 70%, J = 6.6), 7.35 (m, 5 ArH); $^{13}C$ NMR: 17.1 (70%), 17.3 (30%), 19.3 (30%), 22.6 (70%), 31.0, 46.1 (30%), 46.9 (70%), 50.8 (30%), 51.8 (70%), 116.9 (30%), 117.3 (70%), 128.0, 128.3, 128.9, 135.3 (70%), 135.4 (30%), 140.8, 168.1, 177.3; $[\alpha]_D$ -165.3 (c 1, $CHCl_3$); GC-MS (EI, 70 eV): *m/z* 245 ($M^+$), 230, 161, 146, 129, 128, 105, 91, 77. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.39; H, 7.78; N, 5.69.

**Oxidative Cyclisation of *N*-Allylamides (5 - 7). General Procedure.** To a stirred suspension of $Mn(OAc)_3 \cdot 2H_2O$ (2.4 g; 9 mmol) and $Cu(OAc)_2 \cdot H_2O$ (0.9 g; 4.5 mmol) in glacial acetic acid (30 ml) were added the amides **5 - 7** (4.5 mmol) dissolved in glacial acetic acid (5 ml), and the reaction mixture was stirred for 12 h at room temperature. Water was added, followed by $Na_2S_2O_3$ 10% solution (30 ml). The mixture was extracted with ethyl acetate (3 x 150 ml), the organic phase was washed with saturated $NaHCO_3$ solution and dried ($MgSO_4$). After removal of the solvent under reduced pressure the residue was purified by chromatography on silica gel (cyclohexane:ethyl acetate 70:30) to give the bicyclic compounds **8 - 10** as colorless oils.

**Methyl (1*R*,5*R*,1'*R*)-3-Aza-2-oxo-3-(1'-phenylethyl)bicyclo[3.1.0]hexane-1-carboxylate (8a) and its (1*S*,5*S*,1'*R*)-Isomer (8b).** The pure isolated diastereomers were obtained in 44% overall yield as colorless oils. Diastereomeric ratio **8a:8b** 67:33. IR ($CHCl_3$): 1716, 1665 $cm^{-1}$. **(1*R*,5*R*,1'*R*)-Isomer 8a**: $R_f$ = 0.33; $^1H$ NMR: 1.05 (dd, 1H, $H_Z$, $J_{YZ}$ = 4.5, $J_{XZ}$ = 4.5), 1.41 (d, 3H, J = 7.1), 1.93 (dd, 1H, $H_Y$, $J_{YZ}$ = 4.5, $J_{XY}$ = 4.5), 2.27 (m, 1H, $H_X$), 3.06 (dd, 1H, $H_A$, $J_{AB}$ = 10.8, $J_{AX}$ = 5.2), 3.15 (d, 1H, $H_B$, $J_{AB}$ = 10.8), 3.78 (s, 3H), 5.43 (q, 1H, J = 7.1), 7.12 - 7.38 (m, 5 ArH); $^{13}C$ NMR: 16.8, 21.7, 23.3, 32.3, 43.1, 49.5, 53.1, 127.5, 127.9, 128.2, 128.6, 139.7, 169.2, 169.8; $[\alpha]_D$ 102.9 (c 1, $CHCl_3$). **(1*S*,5*S*,1'*R*)-Isomer 8b**: $R_f$ = 0.38; $^1H$ NMR: 0.85 (dd, 1H, $H_Z$, $J_{YZ}$ = 4.4, $J_{XZ}$ = 4.8), 1.53 (d, 3H, J = 7.2), 1.81 (dd, 1H, $H_Y$, $J_{YZ}$ = 4.4, $J_{XY}$ = 8.0), 2.27 (m, 1H, $H_X$), 2.85 (d, 1H, $H_A$, $J_{AB}$ = 10.3), 3.50 (dd, 1H, $H_B$, $J_{BX}$ = 5.8, $J_{AB}$ = 10.3), 3.80 (s, 3H), 5.45 (q, 1H, J = 7.2), 7.15 - 7.42 (m, 5 ArH); $^{13}C$ NMR: 16.0, 20.5, 22.9, 32.2, 42.7, 49.1, 53.0, 127.5, 128.1, 128.2, 129.1, 140.7, 169.2,169.8; $[\alpha]_D$ 147.4 (c 1, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 259 ($M^+$), 244, 227, 212, 199, 186, 168, 144, 120, 105, 91, 77. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.44; H, 6.58; N, 5.36.

**Methyl (1*S*,5*S*,1'*S*)-3-Aza-2-oxo-3-(1'-phenylethyl)-bicyclo[3.1.0]hexane-1-carboxylate (9a) and its (1*R*,5*R*,1'*S*)-Isomer (9b).** The pure isolated diastereomers were obtained in 42% overall yield as colorless oils. Diastereomeric ratio **9a:9b** 67:33. **(1*S*,5*S*,1'*S*)-Isomer 9a:** $[\alpha]_D$ -103.2 (c 1, $CHCl_3$). **(1*R*,5*R*,1'*S*)-Isomer 9b:** $[\alpha]_D$ -147.4 (c 1, $CHCl_3$). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.41; H, 6.56; N, 5.35.

**(1*R*,5*S*,1'*S*)-1-Acetyl-3-aza-2-oxo-3-(1'-phenylethyl)-bicyclo[3.1.0]hexane (10a) and its (1*S*,5*R*,1'*S*)-Isomer (10b).** The diastereomers were obtained as an unseparable mixture in 47% yield. Diastereomeric ratio **10a:10b** 67:33. IR ($CHCl_3$): 1714, 1663 $cm^{-1}$. **(1*R*,5*S*,1'*S*)-Isomer 10a**: $^1H$ NMR: 1.06 (dd, 1H, $H_Z$, $J_{XZ}$ = 5.4, $J_{YZ}$ = 4.0), 1.48 (d, 3H, J = 7.2), 1.93 (dd, 1H, $H_Y$, $J_{XY}$ = 8.1, $J_{YZ}$ = 4.0), 2.32 (m, 1H), 2.59 (s, 3H), 3.06 (dd, 1H, $H_A$, $J_{AX}$ = 5.6, $J_{AB}$ = 10.4), 3.16 (d, 1H, $H_B$, $J_{AB}$ = 10.4), 5.43 (q, 1H, J = 7.2), 7.15 - 7.43 (m, 5 ArH); $^{13}C$ NMR: 16.9, 23.9, 24.8, 30.2, 39.9, 43.1, 49.5, 127.7, 128.2, 129.1, 139.8, 171,1. **(1*S*,5*R*,1'*S*)-Isomer 10b:** $^1H$ NMR: 0.86 (dd, 1H, $H_Z$, $J_{XZ}$ = 5.4, $J_{YZ}$ = 4.0), 1.55 (d, 3H, J = 7.2), 1.81 (dd, 1H, $H_Y$, $J_{XY}$ = 7.6, $J_{YZ}$ = 4.0), 2.32 (m, 1H), 2.61 (s, 3H), 2.87 (d, 1H, $H_A$, $J_{AB}$ = 10.1), 3.48 (dd, 1H, $H_B$, $J_{BX}$ = 5.7, $J_{AB}$ = 10.1), 5.43 (q, 1H, J = 7.2), 7.15 - 7.43 (m, 5 ArH); $^{13}C$ NMR: 16.2, 23.9, 25.4, 30.2, 39.7, 42.9, 49.3, 127.3, 128.2, 129.1, 140.7, 171.1. GC-MS (EI, 70 eV): *m/z* 243 ($M^+$), 228, 215, 200, 186, 144, 132, 120, 105, 91, 77. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.99; H, 7.00; N, 5.73.

**(1*S*,5*R*,1'*R*)-3-Aza-1-hydroxymethyl-2-oxo-3-(1'-phenylethyl)bicyclo[3.1.0]hexane (11a).** A solution of $LiBH_4$ (2M in THF; 3 ml; 6 mmol) was slowly added to a solution of the ester **9a** (2.6 g; 10 mmol) in dry THF (20 ml) at -15 °C and the mixture was stirred at -15 °C for 1 h. Afterwards, the reaction was quenched by addition of 50 ml of saturated $NH_4Cl$ aqueous solution and extracted with ethyl acetate (3 x 100 ml). After drying ($Na_2SO_4$) and removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography (ethyl acetate), to give 1.8 g of **11a** (78% yield). White solid: m.p. 58 - 60 °C. IR ($CHCl_3$): 3345, 1680 $cm^{-1}$; $^1H$ NMR: 0.72 (dd, 1H, $H_Z$, $J_{XZ}$ = 4.7, $J_{YZ}$ = 4.7), 1.14 (dd, 1H, $H_Y$, $J_{XY}$ = 4.7, $J_{YZ}$ = 7.7), 1.25 (br s, 1H, OH), 1.42 (d, 3H, J = 7.2), 1.81 (m, 1H, $H_X$), 3.05 (dd, 1H, $H_A$, $J_{AX}$ = 5.6, $J_{AB}$ = 10.5), 3.16 (d, 1H, $H_B$, $J_{AB}$ = 10.5), 3.82 (ABq, 2H, J = 12.0), 5.42 (q, 1H, J = 7.2), 7.15 - 7.45 (m, 5 ArH); $^{13}C$ NMR: 17.2, 17.4, 30.2, 33.0, 44.4, 49.3, 62.8, 127.7, 128.1, 128.9, 129.1, 175.1. $[\alpha]_D$ 156.3 (c 1, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 231 ($M^+$), 219, 216, 204, 160, 146, 105, 91, 77. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.66; H, 7.35; N, 5.99.

**(1*R*,5*S*,1'*R*)-3-Aza-1-hydroxymethyl-2-oxo-3-(1'-phenylethyl)bicyclo[3.1.0]hexane (11b).** Starting from **8b** (2.1 g; 8 mmol), the compound **11b** was obtained (1.4 g; 76% yield) following the procedure used for preparing **11a**. White crystals (cyclohexane-$CH_2Cl_2$): m.p. 129 - 131 °C. IR ($CHCl_3$): 3345, 1685 $cm^{-1}$; $^1H$ NMR: 0.53 (dd, 1H, $H_Z$, $J_{XZ}$ = 4.5, $J_{YZ}$ = 4.5), 1.02 (dd, 1H, $H_Y$, $J_{YZ}$ = 4.5, $J_{XY}$ = 7.7), 1.25 (br s, 1H, OH), 1.53 (d, 3H, J = 7.2), 1.82 (m, 1H, $H_X$), 2.87 (d, 1H, $H_A$, $J_{AB}$ = 10.3), 3.47 (dd, 1H, $H_B$, $J_{BX}$ = 5.9, $J_{AB}$ = 10.3), 3.84 (ABq, 2H, $J_{AB}$ = 12.1), 5.37 (q, 1H, J = 7.2), 7.15 - 7.39 (m, 5 ArH); $^{13}C$ NMR: 16.4, 16.6, 31.4, 32.7, 44.2, 49.0, 62.8, 127.3, 128.0, 129.0, 141.0, 175.3; $[\alpha]_D$ 135.1 (c 1, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 231 ($M^+$), 219, 216, 204, 160, 146, 105, 91, 77. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.64; H, 7.36; N, 6.02.

**(1*S*,5*R*,1'*S*)-3-Aza-1-*t*-butoxycarbonylamino-2-oxo-3-(1'-phenylethyl)bicyclo[3.1.0]hexane (13a).** A suspension of compound **9a** (1.3 g; 5 mmol) in 2M NaOH (40 ml) was stirred for 4 h at r.t. The mixture was then extracted with ethyl acetate (100 ml) and then the aqueous layer was acidified with 2M HCl (50 ml). After extraction with ethyl acetate (3 x 100 ml), drying and removal of the solvent under reduced pressure, **(1*S*,5*S*,1'*S*)-3-aza-2-oxo-3-(1'-phenylethyl)bicyclo[3.1.0]hexane-1-carboxylic acid 12a** was obtained (1.16 g; 95% yield) as a colorless oil and

was used without further purification: $^1$H NMR: 1.26 (dd, 1H, $H_Z$, $J_{XZ}$ = 4.5, $J_{YZ}$ = 4.5), 1.58 (d, 3H, J = 7.0), 1.84 (dd, 1H, $H_Y$, $J_{YZ}$ = 4.5, $J_{XY}$ = 4.5), 2.58 (m, 1H, $H_X$), 3.12 (dd, 1H, $H_A$, $J_{AX}$ = 5.2, $J_{AB}$ = 10.8), 3.25 (d, 1H, $H_B$, $J_{AB}$ = 10.8), 5.32 (q, 1H, J = 7.0), 7.15 - 7.42 (m, 5 ArH), 8.1 (br s, 1H, OH); $^{13}$C NMR: 16.1, 22.2, 23.9, 37.2, 43.9, 50.4, 127.4, 128.1, 129.1, 140.6, 170.6, 171.5.

The crude carboxylic acid **12a** (1.16 g; 4.7 mmol) and triethylamine (0.8 ml; 5.6 mmol) were mixed with dry *t*-BuOH (50 ml) at 25 °C under argon atmosphere. Then diphenylphosphoryl azide (1.4 g; 5.2 mmol) was added and the reaction mixture was stirred under reflux for 12 h. The solution was concentrated and the crude product was extracted with ethyl acetate (2 x 100 ml), washed with $H_2O$ and brine and dried ($Na_2SO_4$). After evaporation of the solvent, the residue was separated by flash chromatography (cyclohexane:ethyl acetate 50:50), to give **13a** (0.53 g; 36% yield) as a colorless oil. IR ($CHCl_3$):1730, 1683 cm$^{-1}$; $^1$H NMR: 0.83 (dd, 1H, $H_Z$, $J_{XZ}$ = 4.9, $J_{YZ}$ = 4.9), 1.25 (dd, 1H, $H_Y$, $J_{XY}$ = 5.2, $J_{YZ}$ = 4.9), 1.39 (d, 3H, J = 7.2), 1.41 (s, 9H), 2.12 (m, 1H, $H_X$), 3.05 (dd, 1H, $H_A$, $J_{AX}$ = 5.2, $J_{AB}$ = 15.5), 3.14 (d, 1H, $H_B$, $J_{AB}$ = 15.5), 5.37 ( q, 1H, J = 7.2), 5.64 (br s, 1H, NH), 7.15 - 7.41 (m, 5 ArH); $^{13}$C NMR: 17.2, 19.1, 19.6, 28.7, 41.0, 43.4, 49.5, 80.5, 128.3, 128.6, 129.0, 139.8, 156.1, 172.7. $[\alpha]_D$ -116.6 (c 1, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 316 ($M^+$), 260, 248, 216, 201, 170, 134, 120, 111, 105, 91, 77. Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.27; H, 7.61; N, 8.77.

**(1*R*,5*S*,1'*S*)-3-Aza-1-*t*-butoxycarbonylamino-2-oxo-3-(1'-phenylethyl)bicyclo[3.1.0]hexane (13b) and (1*R*,5*S*,1'*S*)-3-Aza-1-azidocarbonylamino-2-oxo-3-(1'-phenylethyl)bicyclo[3.1.0]hexane (14).** Starting from **9b** (1.7 g; 6.5 mmol), **(1*R*,5*R*,1'*S*)-3-aza-2-oxo-3-(1'-phenylethyl)bicyclo[3.1.0]hexane-1-carboxylic acid 12b** was obtained (1.5 g; 94% yield) as a colorless oil following the procedure described above for **13a** and was used without further purification: $^1$H NMR: 1.02 (dd, 1H, $H_Z$, $J_{XZ}$ = 4.8, $J_{YZ}$ = 4.4), 1.45 (d, 3H, J = 7.0), 1.92 (dd, 1H, $H_Y$, $J_{XY}$ = 5.0, $J_{YZ}$ = 4.4), 2.68 (m, 1H, $H_X$), 2.98 (d, 1H, $H_A$, $J_{AB}$ = 10.3), 3.51 (dd, 1H, $H_B$, $J_{BX}$ = 5.8, $J_{AB}$ = 10.3), 5.34 (q, 1H, J = 7.0), 7.12 - 7.41 (m, 5 ArH), 8.03 (br s, 1H, OH); $^{13}$C NMR: 17.1, 21.3, 24.9, 37.2, 43.9, 50.4, 127.3, 128.3, 129.0, 140.5, 163.6, 164.2. The crude carboxylic acid **12b** (1.5 g; 6 mmol) and triethylamine (1.0 ml; 7.2 mmol) were mixed with dry *t*-BuOH (50 ml) at 25 °C under argon atmosphere. Then diphenylphosphoryl azide (1.8 g; 6.6 mmol) was added and the reaction mixture was stirred under reflux for 12 h. The solution was concentrated and the crude product was extracted with ethyl acetate (2 x 100 ml), washed with $H_2O$ and brine and dried ($Na_2SO_4$). After evaporation of the solvent, the residue was separated by flash chromatography (cyclohexane:ethyl acetate 50:50), to give first **13b** (0.68 g; 36% yield) as a colorless oil. IR ($CHCl_3$):1735, 1680 cm$^{-1}$; $^1$H NMR: 0.63 (dd, 1H, $H_Z$, $J_{XZ}$ = 5.1, $J_{YZ}$ = 5.1), 1.20 (dd, 1H, $H_Y$, $J_{YZ}$ = 5.1, $J_{XY}$ = 8.1), 1.44 (s, 9H), 1.54 (d, 3H, J = 7.1), 1.91 - 2.15 (m, 1H, $H_X$), 2.83 (d, 1H, $H_A$, $J_{AB}$ = 10.5), 3.61 (dd, 1H, $H_B$, $J_{BX}$ = 5.9, $J_{AB}$ = 10.5), 5.38 (q, 1H, J = 7.1), 5.78 (br s, 1H, NH), 7.15 - 7.39 (m, 5 ArH); $^{13}$C NMR: 16.3, 17.7, 19.2, 28.8, 40.9, 43.3, 49.8, 80.3, 127.4, 127.7, 128.1, 129.0, 140.7, 158.1, 172.0. $[\alpha]_D$ -139.6 (c 1, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 316 ($M^+$), 260, 248, 216, 201, 170, 134, 120, 111, 105, 91, 77. Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.26; H, 7.59; N, 8.78.

Further elution with ethyl acetate gave **(1*R*,5*S*,1'*S*)-3-aza-1-azidocarbonylamino-2-oxo-3-(1'-phenylethyl)bicyclo[3.1.0]hexane 14** (0.22 g; 13% yield). White crystals (cyclohexane-$CH_2Cl_2$): m.p. 160 - 162 °C. IR ($CHCl_3$): 2125, 1778, 1685 cm$^{-1}$; $^1$H NMR: 0.61 (dd, 1H, $H_Z$, $J_{XZ}$ = 5.1, $J_{YZ}$ = 5.1), 1.27 (dd, 1H, $H_Y$, $J_{YZ}$ = 5.1,

$J_{XY}$ = 8.4), 1.57 (d, 3H, J = 7.1), 2.09 (m, 1H, $H_X$), 2.85 (d, 1H, $H_A$, $J_{AB}$ = 10.5), 3.68 (dd, 1H, $H_B$, $J_{BX}$ = 5.9, $J_{AB}$ = 10.5), 5.39 (q, 1H, J = 7.1), 7.09 - 7.41 (m, 5 ArH), 7.99 (s, 1H, NH); $^{13}$C NMR: 16.2, 17.6, 19.2, 40.9, 43.4, 49.9, 127.2, 128.1, 129.1, 140.7, 158.2, 172.2. $[\alpha]_D$ -115.4 (c 1, $CHCl_3$). GC-MS (EI, 70 eV): *m/z* 285 ($M^+$), 242, 227, 215, 165, 132, 120, 105, 91, 77. Anal. Calcd for $C_{14}H_{15}N_5O_2$: C, 58.94; H, 5.30; N, 24.55. Found: C, 58.86; H, 5.24; N, 24.49.

**X-Ray Crystal Structure Analysis.** Crystal Data: **Compound 11b**, $C_{14}H_{17}NO_2$, M = 231.30, Monoclinic, Space group $P2_1$, a = 6.177(4) Å, b = 8.541(1) Å, c = 11.554(6) Å, β = 96.55(3) °, V = 605.6(5) Å$^3$, Z = 2, D(calc) = 1.27 g/cm$^3$. **Compound 14**, $C_{14}H_{15}N_5O_2$, M = 285.31, Monoclinic, Space group $P2_1$, a = 8.889(1) Å, b = 6.265(1) Å, c = 13.500(2) Å, β = 98.53(1) °, V = 744.5(3) Å$^3$, Z = 2, D(calc) = 1.27 g/cm$^3$. 1955 (**11b**) and 2036 (**14**) reflections were collected on a CAD4 Enraf-Nonius single crystal diffractometer at room temperature by ω scan technique by using graphite-monochromated MoKα radiation (λ = 0.7107 Å). The structures were solved using direct methods and refined through full-matrix least-squares methods using 1569 observed reflections with $I \geq 3\sigma(I)$ for **11b** and 1295 observed reflections with $I \geq \sigma(I)$ for **14**. The non-hydrogen atoms were treated anisotropically. The hydrogen atoms were calculated from the carbon positions and added as fixed contributions with isotropic thermal parameters of 1.3 times the value of $B_{eq}$ of the atoms to which they are attached. R = 0.040 and Rw = 0.038 for **11b** and R = 0.059 and Rw = 0.037 for **14**. The ORTEP drawings [17] are shown in Figures. 1 and 2 together with the atom numbering scheme. In Figure 4 is shown the crystal packing with the hydrogen-bonding scheme of structure **11b**. Calculations were carried out on a VAX 2000 by using the Molen package. [18] Atom coordinates, anisotropic thermal parameters and tables of bond lengths and angles are deposited at the Cambridge Crystallographic Data Centre, University Chemical Laboratory Lensfield Road, Cambridge CB2 1EW, UK.

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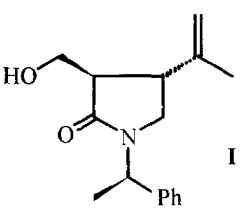
**15.** This behaviour must be ascribed to the constrained bicyclic system. In fact we prepared the compound **I** and the $\Delta\nu$ of the $C\underline{H}_2OH$ pattern remained unchanged even on changing the concentration of the sample.




**I**

$^1$H NMR: 1.55 (d, 3H, J = 7.2), 1.62 (s, 3H), 2.60 - 2.84 (m, 3H, $H_A$ + $H_X$ + $H_Y$), 3.22 (br s, 1 H, OH), 3.34 - 3.44 (m, 1H, $H_B$), 3.71 (dd, 1H, J = 6.8, J = 11.1), 3.92 (dd, 1H, J = 4.2, J = 11.1), 4.79 (m, 2H), 5.50 (q, 1H, J = 7.2), 7.18 - 7.41 (m, 5 ArH).

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