α,γ -Diamino acids: Asymmetric Synthesis of New Constrained 6-Amino-3-aza-bicyclo[3.2.1]octane-6-carboxylic Acids

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Table of Contents of Supporting Information:

1. General	S2
2. NMR discussion for compounds 5a	S3
3. ^1H and ^{13}C NMR spectra of compounds 2-10	S5-S25

1. General

Melting points were determined using a capillary apparatus. ^1H NMR spectra were recorded on 200 or 500 MHz spectrometers. Coupling constants (J) are given in Hertz (Hz). TLC analyses were performed on ready-to-use silica gel plates. Column chromatography was performed on silica gel [Kieselgel 60-70 230 ASTM] with the solvents indicated. IR spectra were taken with a FT-IR spectrophotometer.

Compounds *exo-1a*,⁶ *endo-1a*,⁶ *exo-1b*^{3b} and *endo-1b*^{3b} were prepared according to known procedures.

2. NMR discussion for compounds **5a**

All compounds were characterized by spectroscopic data (^1H NMR, ^{13}C NMR, COSY, NOESY, Hetcor) and, as examples, the spectra of compounds **5** are here detailed. A predominant chair-envelope conformation for 3-azabicyclo[3.2.1]octane ring was suggested⁷ in which the piperidine ring possesses a chair conformation. In particular, this hypothesis is confirmed by X-Ray analysis of 3-benzyl-3-azabicyclo[3.2.1]octane from which it is evicted that the benzyl group is in the equatorial position.⁸ Accordingly, we assumed that the more probable conformation of compounds **5** is that shown in Figure S1.

Figure S1. Conformation and selected NOESY interactions for compounds **5a**.

exo-5a X = NHCOMe; Y = CO₂Me
endo-5a X = CO₂Me; Y = NHCOMe

Typical signals for compound *exo-5a* are at δ 1.50 ($\text{H}_{\text{eq}}\text{-8}$) and 2.00 ($\text{H}_{\text{ax}}\text{-8}$) and at δ 2.20 (H-1) e 2.72 (H-5). Methylene protons resonate at δ 2.35 ($\text{H}_{\beta}\text{-2}$), 2.80 ($\text{H}_{\alpha}\text{-2}$), 2.00 ($\text{H}_{\beta}\text{-4}$), 2.53 ($\text{H}_{\alpha}\text{-4}$), 2.35 ($\text{H}_{\text{x}}\text{-7}$), 1.72 ($\text{H}_{\text{n}}\text{-7}$) confirming the formation of constrained ring. An AB system at 3.55, 3.17 δ ($J = 12.5$ Hz) characterizes the presence of the benzyl protons. Selected signals in the ^{13}C NMR spectrum are at δ 65.9 (C-6), 62.2 (CH_2Ar), 61.0 (C-2), 55.6 (MeOAr), 54.9 (C-4), 52.5 (OMe), 43.0 (C-7), 40.0 (C-5), 37.1 (C-8), 34.7 (C-1), 22.5 (MeCO). ^1H NMR spectrum of diastereomer *endo-5a* shows signals at δ 3.42, 3.33 (CH_2Ar), 3.01 ($\text{H}_{\text{n}}\text{-7}$), 1.90 ($\text{H}_{\text{x}}\text{-7}$), 2.84 ($\text{H}_{\alpha}\text{-4}$), 2.18 ($\text{H}_{\beta}\text{-4}$), 2.71 ($\text{H}_{\alpha}\text{-2}$), 2.02 ($\text{H}_{\beta}\text{-4}$), 2.27 (H-1), 2.19 (H-5), 2.01 ($\text{H}_{\text{ax}}\text{-8}$), 1.51 ($\text{H}_{\text{eq}}\text{-8}$). The equatorial position of H-8 was unequivocally assigned through a Cosy experiment. In fact, it is evidenced a coupling with $\text{H}_{\text{n}}\text{-7}$ at 3.0 ($J = 1.8$ Hz). The carbon atoms resonate at δ 68.5 (C-6), 62.0 (CH_2Ar), 59.0 (C-2), 55.9 (C-4), 55.6 (MeOAr), 52.5 (OMe), 46.8 (C-5), 39.9 (C-7), 37.1 (C-8), 35.1 (C-1), 23.7 (MeCO). Noesy experiments confirmed the assigned configuration. Significant spacial proximity on

exo-5a was observed between H_{orto} protons of aryl ring at (δ 7.16) and H _{α -2}, H _{α -4}, and most of all, with NH (δ 6.44) and Me of acetamido group (δ 1.59). Overhauser effect was observed in compound *endo-5a* between H_{orto} protons on aryl ring (7.26 δ) and proton of CH₂ groups at lower field (H _{α -2}: 2.71; H _{α -4}: 2.84; H_{n-7}: 3.01 δ) and Me group of carboxylic function (3.69 δ). Furthermore, the NH group shows an Overhauser effect with H_{ax-8}.

3. ^1H and ^{13}C NMR spectra of compounds 2-10

^1H -NMR spectrum of compound **exo-2a**

^{13}C -NMR spectrum of compound **exo-2a**

^1H -NMR spectrum of compound **endo-2a**

^{13}C -NMR spectrum of compound **endo-2a**

^1H -NMR spectrum of compound **exo-2b**

^{13}C -NMR spectrum of compound **exo-2b**

^1H -NMR spectrum of compound **endo-2b**

^{13}C -NMR spectrum of compound **endo-2b**

^1H -NMR spectrum of compound **3a**

^{13}C -NMR spectrum of compound **3a**

^1H -NMR spectrum of compound **3b**

^{13}C -NMR spectrum of compound **3b**

^1H -NMR spectrum of compound **4a**

^{13}C -NMR spectrum of compound **4a**

^1H -NMR spectrum of compound **4b**

^{13}C -NMR spectrum of compound **4b**

^1H -NMR spectrum of compound **exo-5a**

^{13}C -NMR spectrum of compound **exo-5a**

^1H -NMR spectrum of compound **exo-5b**

^{13}C -NMR spectrum of compound **exo-5b**

^1H -NMR spectrum of compound **endo-5a**

^{13}C -NMR spectrum of compound **endo-5a**

^1H -NMR spectrum of compound **endo-5b**

^{13}C -NMR spectrum of compound **endo-5b**

^1H -NMR spectrum of compound **exo-6a**

^{13}C -NMR spectrum of compound **exo-6a**

^1H -NMR spectrum of compound **endo-6a**

^{13}C -NMR spectrum of compound **endo-6a**

^1H -NMR spectrum of compound **exo-7**

^{13}C -NMR spectrum of compound **exo-7**

^1H -NMR spectrum of compound **endo-7**

^{13}C -NMR spectrum of compound **endo-7**

^1H -NMR spectrum of compound **exo-8**

^{13}C -NMR spectrum of compound **exo-8**

¹H-NMR spectrum of compound **endo-8**

¹³C-NMR spectrum of compound **endo-8**

¹H-NMR spectrum of compound **exo-9**

¹³C-NMR spectrum of compound **exo-9**

^1H -MR spectrum of compound **endo-9**

^{13}C -NMR spectrum of compound **endo-9**

^1H -NMR spectrum of compound **exo-10**

^{13}C -NMR spectrum of compound **exo-10**