Synthesis A. López-Rodríguez et al. Feature

Synthesis of Novel Iminosugar Derivatives Based on a 2-Azabicyclo[4.1.0]heptane Skeleton

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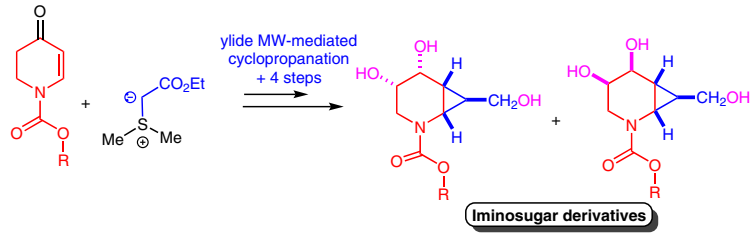

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Abstract Iminosugars are good starting points for the development of different kinds of drugs. Many are polyhydroxylated piperidines that behave as biomimetics of their corresponding pyranoses analogues. In the interaction with carbohydrate processing enzymes, selectivity is a crucial issue and the benefits of introducing a cyclopropane bridge in a piperidine structure is demonstrated. The synthesis of novel bicyclic piperidine-based iminosugars using a sulfur ylide cyclopropanation as the key synthetic step is described.

Key words bicyclic compounds, piperidines, stereoselective synthesis, ylides, iminosugars, cyclopropanation

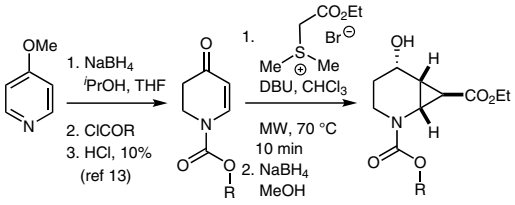
Glycosidases play a crucial role in many important biological processes.[1] The design and synthesis of new glycosidase inhibitors opens the possibility of finding new therapeutic targets for the treatment of diabetes, AIDS, or cancer.[2] In pursuing this goal, adequate metabolic stability and conformational mimicking of monosaccharides is needed as well as achieving enough selectivity towards specific glycosidases. Iminosugars are a family of natural and synthetic aza-heterocycles with great similarity to carbohydrates, thus being able to compete with carbohydrates for the active site of glycosidases.[3] They share with sugars the presence of various stereogenic centers so that they can be highly specific and may be useful in modulating the activity of several glycosidases. The replacement of the oxygen in the ring by a nitrogen maintains their absorption and cellular transportation mechanism. In addition, this basic nitrogen is protonated at physiological pH and mimics the intermediate formed during the hydrolysis of the glycosidic bond and various hydroxyl groups. Many iminosugars introduce a conformationally restricting motif that adds selectivity to a particular enzyme. Up to now, several competitive inhibitors of these enzymes are being developed as new drugs. Miglitol (Glyset®)[4] and miglustat (Zavesca®),[5] for instance, are being commercialized for the treatment of diabetes type II and as the first oral treatment for Gaucher disease, respectively.

Several groups have studied the synthesis of iminosugars with a great emphasis on the preparation of piperidine derivatives.[6] Many of these polyhydroxylated piperidine derivatives are related to natural iminosugar nojirimycin, and its 1-deoxyanalogues deoxynojirimycins, which were isolated and characterized from natural sources.[7] Lack of the 1-hydroxy group in the latter improves their stability in the biological environment. Different stereoisomers of deoxynojirimycin, are powerful inhibitors of glycosidases. Many derivatives and analogues of this family have also been synthesized.[8]

As a novel approach to improve selectivity of iminosugras we envisioned the possibility of rigidifying the piperidine structure by including a cyclopropanic bridge.[9] We have designed new bicyclic iminosugars that include the cyclopropane motif aimed to fix the conformation, and hopefully improve the biological properties in terms of activity and selectivity. The resulting molecules have a flattened-chair conformation as a result of the fusion with the cyclopropane ring. The only previous work in which a cyclopropane ring was included in the structure was disclosed by Shipman.[10] In addition, very recently, derivatives of iminosugars possessing carbamate groups have been described.[11] Carbamates are relevant pharmacophores present for instance in antibiotics active against Gram-positive bacteria.[12] Thus, we have introduced in our structures two different carbamate groups, that may contribute to give interesting biological properties to the new compounds, or could be eliminated readily in further stages.

In this work, we present the synthesis of these new bicyclic iminosugars. The key cyclopropanation step and subsequent functional group modifications will give us different stereoisomers of the desired products.

The first step was the synthesis of enaminones **1a**,**b**. These enaminones are well-known building blocks that have received wide synthetic attention.[13] We selected the procedure described by Minnaard and Feringa to transform 4-methoxypyridine into **1a**,**b** although we used $NaBH_4$ as the reducing agent.[14] Similar yields as in the literature were achieved. The next step was the sulfur ylide-mediated cyclopropanation, which was carried out using our recently disclosed procedure under microwave heating. This method allows for the generally long reaction times used for these transformations to be shortened.[15] Thus, after the reaction of **1a**,**b** with (2-ethoxy-2-oxoethyl)dimethylsulfonium bromide using DBU as the base, the resulting products were reduced with $NaBH_4$, which gave racemic **2a**,**b** in 57–52% yield, respectively, after the two steps. Interestingly these two products were obtained as a single diastereomer: only the *trans*-cyclopropane was formed and the reduction step proceeded with total stereoselectivity (Scheme 1).

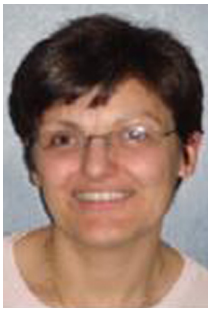


Scheme 1 Synthesis of cyclopropanes **2**

The next step was the dehydration of compounds **2a**,**b**, which was accomplished by seleniation and oxidation–elimination to give **3a**,**b** in good yields (78–83%). From these intermediates, two different *syn*-dihydroxy diastereo-

Biographical sketches

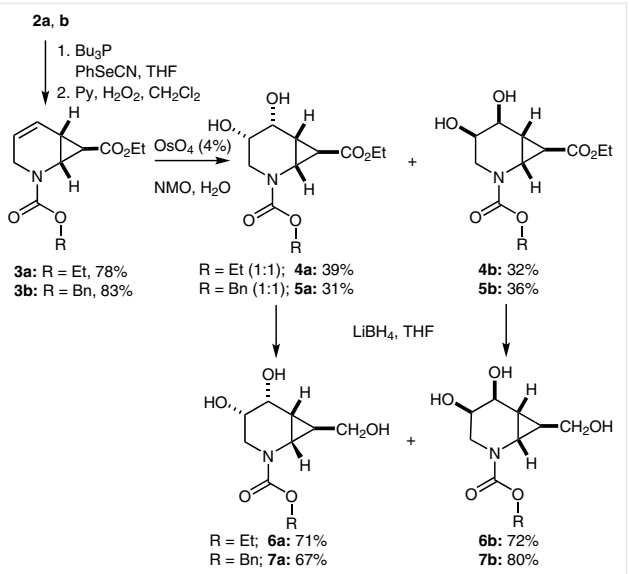
Alberto López Rodríguez was born in Salamanca, Spain, in 1989. He studied chemistry at the Universidad de Salamanca (B.S. in 2012) and obtained a Master's degree in evaluation and development of drugs (B.S. in 2014). He started his Ph.D. at Universidad San Pablo-CEU in 2014 working on metal-catalyzed cyclization reactions, synthesis of new biologically active molecules, and structural studies on biomacromolecules.



Gema Domínguez was born in Madrid, Spain, in 1960. She studied chemistry at the Universidad Complutense de Madrid (B.S. in 1982), where she received her Ph.D. in organic chemistry in 1986. In 2009, she was appointed as full professor at Universidad San Pablo-CEU. She is currently working on metal-catalyzed cyclization, metathesis reactions, and synthesis of new biologically active molecules.

Javier Pérez Castells was born in Madrid, Spain, in 1967. He studied chemistry at the Universidad Complutense de Madrid (B.S. in 1990), where he received his Ph.D. in organic chemistry in 1994. In 2007, he was appointed as full professor at Universidad San Pablo-CEU, where he works on metal-catalyzed cyclization reactions, synthesis of new biologically active molecules, and structural studies on biomacromolecules.

mers were obtained from each substrate by an osmylation reaction, which could be separated and characterized using 2D standard NMR experiments. At this point, we had 4 compounds that were finally reduced using $LiBH_4$ to give compounds **5** (Scheme 2). The final reduction of the ester moiety gave novel trihydroxylated bicyclic iminosugars bearing 5 stereogenic centers, which will be sent for evaluation against glycosidases. Figure 1 shows a three-dimensional model of **6a** where the flattened conformation is shown.



Scheme 2 Synthesis of compounds **6** and **7**

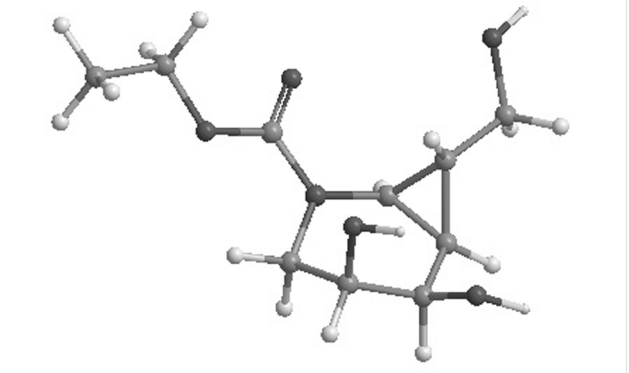


Figure 1 Three-dimensional model of **6a**

In conclusion, we have shown the synthesis of novel rigidified iminosugars bearing a cyclopropane ring, a carbamate substituent, and three hydroxy groups as potential inhibitors of glycosidases. The method described will be used to obtain other highly functionalized frameworks containing the cyclopropane ring as intermediates **3**–**5**, which can be further transformed readily into other derivatives.

Reaction progress was monitored using analytical TLC on Merck silica gel 60 F-254 plates. Visualization was achieved by UV light (254 nm). Cyclopropanation reactions were carried out in a Biotage Initiator+ microwave reactor. NMR spectra were recorded on a Bruker spectrometer (400 MHz for ^{1}H, and 101 MHz for ^{13}C). Chemical shifts are reported in δ ppm referenced to $CDCl_3$ (δ = 7.26 for ^{1}H NMR and 77.00 for ^{13}C NMR) or CD_3OD (δ = 3.31 for ^{1}H NMR and 49.00 for ^{13}C NMR). All the residues were purified by flash chromatography on silica gel. Bidimensional spectra (HMQC, HMBC, COSY, NOESY) were recorded for all compounds in order to carry out the assignment.

Diethyl (1*R**,5*S**,6*R**,7*R**)-5-Hydroxy-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate (2a)

Ethyl 4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (**1a**; 4.53 g, 26.8 mmol) was prepared in 67% yield from 4-methoxypyridine (4 mL, 40.0 mmol), following the procedure described in the literature except that $NaBH_4$ was used as the reducing agent.[14] To a solution of (2-ethoxy-2-oxoethyl)dimethylsulfonium bromide (10.22 g, 44.6 mmol) in $CHCl_3$ (41 mL) was added DBU (6.75 mL, 45.18 mmol). After stirring for 30 min, **1a** (4.53 g, 26.8 mmol) was added and the reaction mixture was heated up to 70 °C through microwave irradiation for 10 min. The mixture was then washed with aq 1 M HCl (30 mL), H_2O (2 × 30 mL), and brine (2 × 30 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum to afford 6.56 g of a crude mixture containing diethyl (1*R**,6*R**,7*R**)-5-oxo-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate. This mixture was dissolved in MeOH (70 mL) and $NaBH_4$ (985 mg, 26.1 mmol) was added in portions at 0 °C. After stirring for 45 min, the reaction was quenched with H_2O (86 mL). The mixture was then extracted with Et_2O (3 × 60 mL) and the combined organic phases were washed with brine (60 mL), dried ($MgSO_4$), filtered, and concentrated. After flash column chromatography [hexane/EtOAc (2:1) → hexane/EtOAc (1:2)], 3.95 g (15.2 mmol, 57%) of pure compound **2a** was obtained as a colorless oil; R_f = 0.2 (hexane/EtOAc, 1:1). The compound was assigned as 1*R**,5*S**,6*R**,7*R** due to the detection of NOESY cross peaks between H5 and H6. NMR spectra showed a mixture of two conformers [67% (α):33% (β)].

IR (ATR): 3442, 3017, 1716, 1689 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.32–4.24 (m, 1 H, H5), 4.20–4.03 (m, 4 H, CH_2CH_3), 3.85 (dt, *J* = 13.1, 3.1 Hz, 1 H, H3, α), 3.71 (dt, *J* = 13.4, 3.8 Hz, 1 H, H3, β), 3.54 (dd, *J* = 8.8, 2.7 Hz, 1 H, H1, β), 3.41 (dd, *J* = 8.8, 2.7 Hz, 1 H, H1, α), 2.80 (m, 2 H, OH + H3 β), 2.71 (t, *J* = 12.7 Hz, 1 H, H3, α), 2.19–2.12 (m, 1 H, H6), 2.03–1.96 (m, 1 H, H4 β), 1.94–1.85 (m, 1 H, H4, α), 1.85–1.78 (m, 1 H, H7), 1.30–1.15 (m, 7 H, $CO_2CH_2CH_3$ + $NCO_2CH_2CH_3$ + H4).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.5 (CO_2, α), 171.4 (CO_2, β), 156.5 (NCO_2, α), 156.1 (NCO_2, β), 63.7 (C5, α), 63.5 (C5, β), 61.7 (CH_2CH_3, α), 61.6 (CH_2CH_3, β), 60.8 (CH_2CH_3, β), 60.7 (CH_2CH_3, α), 41.0 (C3, β), 40.7 (C3, α), 40.6 (C1, β), 40.2 (C1, α), 30.7 (C4, α), 30.5 (C4, β), 27.8 (C6, α), 27.7 (C6, β), 25.2 (C7, α), 24.5 (C7, β), 14.4 (CH_2CH_3), 14.2 (CH_2CH_3, α), 14.0 (CH_2CH_3, β).

Anal. Calcd for $C_{12}H_{19}NO_5$ (257.28): C, 56.0; H, 7.4. Found: C, 56.2; H, 7.0.

2-Benzyl 7-Ethyl (1*R**,5*S**,6*R**,7*R**)-5-Hydroxy-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate (2b)

Benzyl 4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (**1b**; 6.38 g, 27.6 mmol) was prepared from 4-methoxypyridine (4.0 mL, 40.0 mmol) in 69% yield, following the procedure described in the literature except that $NaBH_4$ was used as the reducing agent.[14] The synthesis was continued as for compound **2a** using (2-ethoxy-2-oxoethyl)di-

methylsulfonium bromide (10.0 g, 43.75 mmol) in $CHCl_3$ (45 mL) and DBU (7 mL, 46.00 mmol). After the cyclopropanation step, 7.0 g of crude 2-benzyl 7-ethyl (1*R**,6*R**,7*R**)-5-oxo-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate obtained was treated $NaBH_4$ (1.024 g, 27.1 mmol) in MeOH (70 mL) to give, after isolation and flash column chromatography [hexane/EtOAc (2:1) → hexane/EtOAc (1:2)], 3.67 g (14.35 mmol, 52%) of **2b** as a colorless oil; R_f = 0.1 (hexane/EtOAc, 1:1). This compound was assigned as 1*R**,5*S**,6*R**,7*R** due to the detection of NOESY cross peaks between H5 and H6 and analogy with compound **2a**. NMR spectra showed a mixture of two conformers [66% (α):34% (β)].

IR (ATR): 3460, 3022, 2959, 1699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.27 (m, 5 H, CH Ar), 5.28–5.04 (m, 2 H, CH_2Ar), 4.39–4.28 (m, 1 H, H5), 4.18–4.02 (m, 2 H, $CO_2CH_2CH_3$), 3.94 (dt, *J* = 13.5, 3.7 Hz, 1 H, H3, α), 3.83–3.75 (m, 1 H, H3, β), 3.63 (d, *J* = 9.4 Hz, 1 H, H1, β), 3.54 (d, *J* = 8.8 Hz, 1 H, H1, α), 2.87 (t, *J* = 13.3 Hz, 1 H, H3, β), 2.78 (t, *J* = 13.2 Hz, 1 H, H3, α), 2.20 (m, 1 H, H6), 2.05–1.80 (m, 1 H, H4), 1.87 (dd, *J* = 5.9, 2.7 Hz, 1 H, H7), 1.30–1.21 (m, 4 H, CH_2CH_3 β + H4), 1.20 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3, α).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.3 (CO_2Et), 156.2 (NCO_2), 136.4 (C Ar, α) 135.9 (C Ar, β), 128.5 (CH Ar, α), 128.3 (CH Ar, α), 128.2 (CH Ar, β), 128.0 (CH Ar, β), 127.8 (CH Ar, β), 127.3 (CH Ar, α), 67.8 (*C*H_2Ar, β), 67.3 (*C*H_2Ar, α), 63.7 (C5, α), 63.5 (C5, β), 61.2 (CO_2CH_2, β), 60.8 (CO_2CH_2, α), 41.1 (C3, β), 40.9 (C3, α), 40.7 (C1, β), 40.2 (C1, α), 30.8 (C4, α), 30.4 (C4, β), 27.8 (C6, α), 27.6 (C6, β), 25.3 (C7, α), 24.4 (C7, β), 14.1 (CH_2CH_3, β), 14.1 (CH_2CH_3, α).

Anal. Calcd for $C_{17}H_{21}NO_5$ (319.35): C, 63.9; H, 6.6. Found: C, 64.1; H, 6.3.

Diethyl (1*R**,6*R**,7*R**)-2-Azabicyclo[4.1.0]hept-4-ene-2,7-dicarboxylate (3a)

To a solution of **2a** (1.20 g, 4.7 mmol) in anhyd THF (30 mL) was added Bu_3P (2.40 mL, 9.4 mmol) under an argon atmosphere. The solution was heated up to reflux temperature and a solution of phenyl selenocyanate (1.25 mL, 9.4 mmol in 8.20 mL of anhyd THF) was then added to the reaction mixture. The mixture was then stirred overnight and concentrated under vacuum to give 1.30 g of a crude mixture. This crude was dissolved in CH_2Cl_2 (17 mL) and pyridine (0.55 mL), followed by the addition of 33% H_2O_2 (783 µL), and the mixture was stirred for 10 min. After this time, THF (3 mL) was added and the mixture was stirred for another 30 min. Then, Et_2O (44 mL) was added and the mixture was washed once with 10% aq $Na_2S_2O_4$ (20 mL) and then with H_2O (20 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated under vacuum. After flash column chromatography (hexane/EtOAc, 9:1), 860 mg (3.60 mmol, 78%) of **3a** was obtained as a yellow oil; R_f = 0.2 (hexane/EtOAc, 9:1). NMR spectra showed a mixture of two conformers [60% (α):40% (β)].

IR (ATR): 3022, 2987, 1719 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.08–5.98 (m, 1 H, H5), 5.80–5.72 (m, 1 H, H4, α), 5.71–5.63 (m, 1 H, H4, β), 4.27–4.09 (m, 4 H, CH_2CH_3), 3.99 (dd, *J* = 18.3, 5.0 Hz, 1 H, H3, α), 3.90–3.60 (m, 4 H, 2 × H3 β + H3 α + H1 β), 3.53 (dd, *J* = 8.3, 2.7 Hz, 1 H, H1, α), 2.18–2.11 (m, 1 H, H6), 1.65–1.55 (m, 1 H, H7), 1.27 (t, *J* = 7.0 Hz, 6 H, CH_2CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.7 (CO_2), 156.6 (NCO_2, α), 156.4 (NCO_2, β), 125.2 (C4, α), 123.9 (C4, β), 122.4 (C5, β), 122.1 (C5, α), 61.7 (CH_2CH_3), 60.6 (*C*H_2CH_3), 40.6 (C3, β), 40.1 (C3, α), 36.7 (C1, β), 36.40 (C1, α), 34.7 (C7, α), 34.2 (C7, β), 21.5 (C6, α), 20.6 (C6, β), 14.6 (CH_2CH_3), 14.3 (CH_2CH_3).

Anal. Calcd for $C_{12}H_{17}NO_4$ (239.27): C, 60.2; H, 7.2. Found: C, 60.1; H, 7.5.

2-Benzyl 7-Ethyl (1*R**,6*R**,7*R**)-2-Azabicyclo[4.1.0]hept-4-ene-2,7-dicarboxylate (3b)

Following the same procedure as for **3a**, from **2b** (2.16 g, 6.81 mmol), Bu_3P (3.02 mL, 12.2 mmol), and phenyl selenocyanate (1.67 mL, 13.7 mmol), and after flash column chromatography (hexane/EtOAc, 9:1), 1.70 g (5.65 mmol, 83%) of **3b** was obtained as a yellow oil; R_f = 0.2 (hexane/EtOAc, 9:1). NMR spectra showed a mixture of two conformers [65% (α):35% (β)].

IR (ATR): 2983, 1711, 1699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.28 (m, 5 H, CH Ar), 6.07–5.95 (m, 1 H, H5), 5.83–5.73 (m, 1 H, H4, α), 5.69–5.63 (m, 1 H, H4, β), 5.27–5.12 (m, 2 H, CH_2Ar), 4.19–4.04 (m, 2 H, CH_2CH_3), 4.02 (dd, *J* = 18.5, 5.5 Hz, 1 H, H3, α), 3.95–3.75 (m, 2 H, H3, β), 3.73 (dd, *J* = 8.7, 2.1 Hz, 1 H, H1, β), 3.71–3.61 (m, 1 H, H3, α), 3.58 (dd, *J* = 8.1, 2.7 Hz, 1 H, H1, α), 2.22–2.13 (m, 1 H, H6), 1.67–1.64 (m, 1 H, H7, β), 1.62 (dd, *J* = 5.0, 2.7 Hz, 1 H, H7, α), 1.26 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3, β), 1.21 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3, α).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.5 (CO_2, α), 170.4 (CO_2, β), 156.3 (NCO_2, α), 156.1 (NCO_2, β), 136.5 (C Ar, α), 136.3 (C Ar, β), 128.6 (CH Ar, α), 128.4 (CH Ar, β), 128.4 (CH Ar, α), 128.2 (CH Ar, β), 127.9 (CH Ar, β), 127.4 (CH Ar, α), 125.1 (C4, α), 123.7 (C4, β), 122.4 (C5, β), 122.0 (C5, α), 67.4 (CH_2Ar, β), 67.2 (CH_2Ar, α), 60.7 (CH_2CH_3), 40.7 (C3, β), 40.2 (C3, α), 36.8 (C1, β), 36.3 (C1, α), 34.8 (C7, α), 34.2 (C7, β), 21.5 (C6, α), 20.6 (C6, β), 14.2 (CH_2CH_3, α), 14.1 (CH_2CH_3, β).

Anal. Calcd for $C_{17}H_{19}NO_4$ (301.34): C, 67.8; H, 6.4. Found: C, 68.0; H, 6.7.

Diethyl 4,5-Dihydroxy-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate

To a solution of **3a** (430 mg, 1.80 mmol) in acetone (7.30 mL) were added, sequentially, aq 4% OsO_4 (2.23 mL, 0.36 mmol) and a solution of 4-methylmorpholine *N*-oxide (316.30 mg, 2.70 mmol) in H_2O (316.30 µL). The resulting mixture was stirred overnight at r.t. Then, one spatula of Na_2SO_3 and another of Na_2SO_4 were added and the acetone was evaporated in vacuum. The mixture was then extracted with EtOAc (3 × 3 mL), the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered, and evaporated to give a crude 1:1 mixture of two diastereoisomers. After flash column chromatography (hexane/EtOAc, 1:2), both isomers were separated and characterized.

1*R**,4*S**,5*R**,6*R**,7*R**-Isomer 4a

Yield: 183 mg (0.68 mmol, 39%); colorless oil; R_f = 0.26 (hexane/EtOAc, 1:2). The compound was assigned as 1*R**,4*S**,5*R**,6*R**,7*R** due to strong NOESY cross peaks between H5 and H6. NMR spectra showed a mixture of two conformers [70% (α):30% (β)].

IR (ATR): 3429, 2983, 2920, 1707 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.32–4.28 (m, 1 H, H5), 4.23–4.09 (m, 4 H, CH_2CH_3), 3.74 (dd, *J* = 12.1, 4.1 Hz, 1 H, H3, α), 3.61 (dd, *J* = 11.7, 2.2 Hz, 1 H, H3, β), 3.55–3.45 (m, 2 H, H4 + H1 β), 3.38 (dd, *J* = 8.2, 2.0 Hz, 1 H, H1, α), 3.05 (t, *J* = 11.7 Hz, 1 H, H3, β), 2.99 (t, *J* = 12.1 Hz, 1 H, H3, α), 2.60 (br s, 1 H, OH), 2.19 (t, *J* = 7.2 Hz, 1 H, H6), 1.58 (br s, 1 H, OH), 1.51–1.38 (m, 1 H , H7), 1.27 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3), 1.25 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (major conformer) = 171.0 (CO_2), 156.6 (NCO_2), 67.2 (C4), 64.5 (C5), 62.0 (CH_2CH_3), 60.9 (CH_2CH_3), 41.0 (C3), 36.9 (C1), 27.9 (C6), 26.0 (C7), 14.5 (CH_2CH_3), 14.3 (CH_2CH_3).

Anal. Calcd for $C_{12}H_{19}NO_6$ (273.28): C, 52.7; H, 7.0. Found: C, 53.1; H, 7.3.

1*R,4*R**,5*S**,6*R**,7*R**-Isomer 4b**

Yield: 151 mg (0.56 mmol, 32%); colorless oil; R_f = 0.18 (hexane/EtOAc, 1:2). The compound was assigned as 1*R**,4*R**,5*S**,6*R**,7*R** due to the absence of NOESY cross peaks between H5 and H6. NMR spectra showed a mixture of two conformers [80% (α):20% (β)].

IR (ATR): 3431, 2985, 2921, 1704 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.27–4.08 (m, 6 H, 2 × CH_2CH_3 + H3 + H5), 4.03 (t, *J* = 4.0 Hz, 1 H, H4, α), 3.97 (br s, 1 H, H4, β), 3.52 (d, *J* = 9.3 Hz, 1 H, H1, β), 3.42 (dd, *J* = 8.5, 2.6 Hz, 1 H, H1, α), 2.97 (d, *J* = 13.1 Hz, 1 H, H3, β), 2.86 (d, *J* = 14.0 Hz, 1 H, H3, α), 2.46 (br s, 1 H, C5-OH), 2.37 (br s, 1 H, C4-OH), 2.35 (dd, *J* = 5.8, 2.6 Hz, 1 H, H7), 2.13 (m, 1 H, H6), 1.27 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3), 1.26 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ (major conformer) = 171.7 (CO_2), 157.8 (NCO_2), 67.8 (C4), 64.4 (C5), 61.9 (CH_2CH_3), 60.7 (CH_2CH_3), 46.2 (C3), 39.9 (C1), 26.8 (C7), 26.6 (C6), 14.5 (CH_2CH_3), 14.3 (CH_2CH_3).

Anal. Calcd for $C_{12}H_{19}NO_6$ (273.28): C, 52.7; H, 7.0. Found: C, 52.6; H, 6.8.

2-Benzyl 7-Ethyl 4,5-Dihydroxy-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate

Following the same procedure as for **4**, from **3b** (400 mg, 1.33 mmol), aq 4% OsO_4 (2.69 mL, 0.26 mmol), and 4-methylmorpholine *N*-oxide (230.5 mg, 1.97 mmol) in H_2O (230 μL), a crude 1:1 mixture of two diastereoisomers was obtained, which were separated after flash column chromatography (hexane/EtOAc 1:2) and characterized.

1*R,4*S**,5*R**,6*R**,7*R**-Isomer 5a**

Yield: 138 mg (0.41 mmol, 31%); yellow oil; R_f = 0.35 (hexane/EtOAc, 1:2). The product was assigned as 1*R**,4*S**,5*R**,6*R**,7*R** due to detection of NOESY cross peaks between H5 and H6 and analogy with compound **4a**. NMR spectra showed a mixture of two conformers [80% (α):20% (β)].

IR (ATR): 3427, 2980, 2924, 1702 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 5 H, CH Ar), 5.25–5.08 (m, 2 H, CH_2Ar), 4.29 (br s, 1 H, H5), 4.20–4.02 (m, 2 H, CH_2CH_3), 3.75 (dd, *J* = 12.4, 4.1 Hz, 1 H, H3, α), 3.63 (dd, *J* = 12.4, 4.0 Hz, 1 H, H3, β), 3.55–3.46 (m, 1 H, H4), 3.44 (dd, *J* = 8.2, 2.5 Hz, 1 H, H1), 3.07 (t, *J* = 11.2 Hz, 1 H, H3, β), 3.00 (dd, *J* = 12.4, 10.8 Hz, 1 H, H3, α), 2.84–2.68 (m, 1 H, OH), 2.22–2.15 (m, 1 H, H6), 1.46 (dd, *J* = 6.1, 2.6 Hz, 1 H, H7), 1.29–1.23 (m, 3 H, CH_2CH_3, β), 1.19 (t, *J* = 7.1 Hz, 1 H, CH_2CH_3, α).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.9 (CO_2Et), 156.3 (NCO_2), 136.2 (C Ar, α), 136.0 (C Ar, β), 128.6 (CH Ar, β), 128.5 (CH Ar, α), 128.3 (CH Ar, β), 128.1 (CH Ar, β), 128.0 (CH Ar, α), 127.5 (CH Ar, α), 67.7 (CH_2Ar, β), 67.6 (CH_2Ar, α), 67.1 (C4, α), 67.0 (C4, β), 64.5 (C5), 61.1 ($CO_2CH_2CH_3$, β), 61.0 ($CO_2CH_2CH_3$, α), 41.9 (C3, β), 41.1 (C3, α), 37.2 (C1, β), 36.8 (C1, α), 27.9 (C6, α), 27.4 (C6, β), 26.0 (C7, α), 25.3 (C7, β), 14.1 (CH_2CH_3).

Anal. Calcd for $C_{17}H_{21}NO_6$ (335.35): C, 60.9; H, 6.3. Found: C, 61.0; H, 6.0.

1*S,4*R**,5*S**,6*R**,7*R**-Isomer 5b**

Yield: 156 mg (0.47 mmol, 36%); yellow oil; R_f = 0.3 (hexane/EtOAc, 1:3). The product was assigned as 1*S**,4*R**,5*S**,6*R**,7*R** due to absence of NOESY cross peaks between H5 and H6 and analogy with compound **4b**. NMR spectra showed a mixture of two conformers [75% (α):25% (β)].

IR (ATR): 3433, 2983, 2925, 1707 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.29 (m, 5 H, CH Ar), 5.26–5.10 (m, 2 H, CH_2Ar), 4.21–4.00 (m, 5 H, CH_2CH_3 + H3 + H4 + H5), 3.54 (dd, *J* = 8.4, 2.8 Hz, 1 H, H1, β), 3.48 (dd, *J* = 8.5, 2.6 Hz, 1 H, H1, α), 2.99 (d, *J* = 13.9 Hz, 1 H, H3, β), 2.89 (d, *J* = 14.0 Hz, 1 H, H3, α), 2.39 (dd, *J* = 5.7, 2.6 Hz, 1 H, H7), 2.16–2.09 (m, 1 H, H6), 1.29–1.25 (m, 3 H, CH_2CH_3, β), 1.19 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3, α).

^{13}C NMR (101 MHz, $CDCl_3$): δ (major conformer = 171.5 (CO_2), 157.4 (NCO_2), 136.4 (C Ar), 128.4 (CH Ar), 127.9 (CH Ar), 127.4 (CH Ar), 67.8 (C4), 67.6 (CH_2Ar), 64.3 (C5), 60.8 (CH_2CH_3), 46.3 (C3), 39.8 (C1), 26.8 (C6), 26.5 (C7), 14.1 (CH_2CH_3).

Anal. Calcd for $C_{17}H_{21}NO_6$ (335.35): C, 60.9; H, 6.3. Found: C, 61.0; H, 6.6.

Ethyl (1*S,4*S**,5*R**,6*R**,7*R**)-4,5-Dihydroxy-7-(hydroxymethyl)-2-azabicyclo[4.1.0]heptane-2-carboxylate (6a)**

To a solution of **4a** (150 mg, 0.55 mmol) in THF (2.2 mL) THF was added $LiBH_4$ (36 mg, 1.65 mmol) in portions at 0 °C and the resulting mixture was stirred at r.t. overnight. Then, acidic Amberlite was added, the mixture diluted with MeOH, and filtered to give 89 mg (0.38 mmol, 71%) of pure **6a** as a colorless oil; R_f = 0.1 (EtOAc). NMR spectra showed a mixture of two conformers [60% (α):40% (β)].

IR (ATR): 3398, 3022, 2932, 1680 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 4.24–4.09 (m, 3 H, CH_2CH_3 + H5), 3.63 (dd, *J* = 11.5, 5.8 Hz, 1 H, CHOH), 3.58 (dd, *J* = 12.2, 3.8 Hz, 1 H, H3, α), 3.52 (dd, *J* = 12.1, 4.0 Hz, 1 H, H3, β), 3.46–3.37 (m, 1 H , H4), 3.37–3.28 (m, 1 H, CHOH), 3.02 (dd, *J* = 12.1, 10.4 Hz, 1 H, H3, β), 2.93 (dd, *J* = 12.2, 10.6 Hz, 1 H, H3, α), 2.80–2.74 (m, 1 H, H1), 1.41 (m, 1 H, H6), 1.31–1.25 (m, 3 H, CH_2CH_3), 0.91–0.84 (m, 1 H, H7).

^{13}C NMR (101 MHz, CD_3OD): δ = 158.9 (CO_2, α), 158.5 (CO_2, β), 68.6 (C4, α), 68.4 (C4, β), 66.7 (C5, α), 66.5 (C5, β), 64.0 (CH_2OH, β), 63.7 (CH_2OH, α), 62.9 (CH_2CH_3, β), 62.8 (CH_2CH_3, α), 42.9 (C3, β), 42.3 (C3, α), 34.0 (C1, β), 33.2 (C1, α), 27.5 (C7, α), 27.1 (C7, β), 25.5 (C6, α), 24.9 (C6, β), 15.0 (CH_2CH_3, α), 14.9 (CH_2CH_3, β).

Anal. Calcd for $C_{10}H_{17}NO_5$ (231.25): C, 51.9; H, 7.4. Found: C, 52.2; H, 7.2.

Ethyl (1*S,4*R**,5*S**,6*R**,7*R**)-4,5-Dihydroxy-7-(hydroxymethyl)-2-azabicyclo[4.1.0]heptane-2-carboxylate (6b)**

Following the procedure for the synthesis of **6a**, from **4b** (130 mg, 0.48 mmol) and $LiBH_4$ (31 mg, 1.43 mmol), 75 mg (0.32 mmol, 72%) of pure **6b** was obtained as a colorless oil; R_f = 0.3 (EtOAc/EtOH, 9:1). NMR spectra showed a mixture of two conformers [71% (α):29% (β)].

IR (ATR): 3391, 3020, 2936, 1685 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 4.21–4.09 (m, 2 H, CH_2CH_3), 4.05 (dd, *J* = 6.6, 4.5 Hz, 1 H, H5), 3.96–3.81 (m, 2 H, H4 + H3), 3.61 (dd, *J* = 11.3, 5.9 Hz, 1 H, CHOH, α), 3.54 (dd, *J* = 11.3, 6.5 Hz, 1 H, CHOH, β), 3.39–3.26 (m, 1 H, CHOH), 2.93 (d, *J* = 12.8 Hz, 1 H, H3, β), 2.84 (dd, *J* = 13.4, 1.5 Hz, 1 H, H3, α), 2.81 (dd, *J* = 8.4, 3.1 Hz, 1 H, H1, α), 2.78 (dd, *J* = 8.5, 3.0 Hz, 1 H, H1, β), 1.80–1.72 (m, 1 H, H7), 1.40–1.23 (m, 4 H, H6 + CH_2CH_3).

^{13}C NMR (101 MHz, CD_3OD): δ = 159.8 (CO_2, α), 159.5 (CO_2, β), 69.3 (C4, α), 69.2 (C4, β), 66.3 (C5, α), 66.1 (C5, β), 64.5 (CH_2OH, β), 64.3 (CH_2OH, α), 62.8 (CH_2CH_3, β), 62.7 (CH_2CH_3, α), 47.5 (C3, β), 47.3 (C3, α), 36.6 (C1, β), 35.7 (C1, α), 28.2 (C7, α), 27.8 (C7, β), 22.9 (C6, α), 22.7 (C6, β), 15.0 (CH_2CH_3, α), 14.9 (CH_2CH_3, β).

Anal. Calcd for $C_{10}H_{17}NO_5$ (231.25): C, 51.9; H, 7.4. Found: C, 52.1; H, 7.8.

Benzyl (1*S,4*S**,5*R**,6*R**,7*R**)-4,5-Dihydroxy-7-(hydroxymethyl)-2-azabicyclo[4.1.0]heptane-2-carboxylate (7a)**

Following the procedure for the synthesis of **6a**, from **5a** (91 mg, 0.28 mmol) and $LiBH_4$ (17.7 mg, 0.84 mmol) and after flash column chromatography with hexane/EtOAc (1:19), 58 mg (0.20 mmol, 67%) of **7a** was isolated as a colorless oil; R_f = 0.26 (hexane/EtOAc, 1:4). NMR spectra showed a mixture of two conformers [55% (α):45% (β)].

IR (ATR): 3400, 3025, 2933, 1684 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 5 H, CH Ar), 5.17–5.04 (m, 2 H, C*H*$_2$Ar), 4.24–4.15 (m, 1 H, H5), 3.70–3.60 (m, 1 H, CH*H*OH), 3.67 (dd, *J* = 12.0, 4.3 Hz, 1 H, H3, α), 3.58 (dd, *J* = 12.4, 3.9 Hz, 1 H, H3, β), 3.48–3.42 (m, 1 H, H4), 3.36 (dd, *J* = 6.9, 2.8 Hz, 1 H, CH*H*OH, α), 3.30–3.21 (m, 1 H, CH*H*OH, β), 3.02 (t, *J* = 11.5 Hz, 1 H, H3, β), 2.95 (t, *J* = 11.5 Hz, 1 H, H3, α), 2.77 (dd, *J* = 8.1, 2.9 Hz, 1 H, H1, β), 2.73 (dd, *J* = 8.0, 2.8 Hz, 1 H, H1, α), 1.41 (m, 1 H, H6), 0.90–0.80 (m, 1 H, H7).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.9 (NCO_2, β), 156.7 (NCO_2, α), 136.0 (C Ar, β), 135.9 (C Ar, α), 128.7 (CH Ar), 128.5 (CH Ar), 128.4 (CH Ar), 128.2 (CH Ar), 128.0 (CH Ar), 127.9 (CH Ar), 67.8 (*C*H$_2$Ar, α), 67.6 (*C*H$_2$Ar, β), 67.5 (C4, β), 67.4 (C4, α), 65.3 (C5, β), 65.3 (C5, α), 63.6 (CH_2OH, α), 63.3 (CH_2OH, β), 41.8 (C3, β), 41.2 (C3, α), 33.1 (C1, β), 32.3 (C1, α), 26.6 (C7, α), 26.4 (C7, β), 24.0 (C6, β), 23.4 (C6, α).

Anal. Calcd for $C_{17}H_{21}NO_6$ (293.32): C, 61.4; H, 6.5. Found: C, 61.2; H, 6.3.

Benzyl (1*S,4*R**,5*S**,6*R**,7*R**)-4,5-Dihydroxy-7-(hydroxymethyl)-2-azabicyclo[4.1.0]heptane-2-carboxylate (7b)**

Following the procedure for the synthesis of **6a**, from **5b** (113 mg, 0.35 mmol) and $LiBH_4$ (22.0 mg, 1.04 mmol) and after flash column chromatography with hexane/EtOAc (1:19), 80 mg (0.28 mmol, 80%) of pure **7b** was isolated as a colorless oil; R_f = 0.3 (EtOAc/EtOH, 9:1). NMR spectra showed a mixture of two conformers [60% (α):40% (β)].

IR (ATR): 3395, 3022, 2939, 1690 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 5 H, CH Ar), 5.24–4.98 (m, 2 H, C*H*$_2$Ar), 4.10–3.96 (m, 2 H, H3 + H5), 3.95–3.90 (m, 1 H, H4, α), 3.89–3.84 (m, 1 H, H4, β), 3.70 (dd, *J* = 11.3, 5.6 Hz, 1 H, CH*H*OH, α), 3.59 (dd, *J* = 11.3, 6.8 Hz, 1 H, CH*H*OH, β), 3.30 (dd, *J* = 11.3, 7.4 Hz, 1 H, CH*H*OH, β), 2.95 (dd, *J* = 11.3, 9.0 Hz, 1 H, CH*H*OH, α), 2.88–2.69 (m, 2 H, H3 + H1), 1.87–1.77 (m, 1 H , H7), 1.41–1.26 (m, 1 H, H6).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.9 (NCO_2, α), 157.6 (NCO_2, β), 136.4 (C Ar, β), 136.3 (C Ar, α), 128.5 (CH Ar α), 128.4 (CH Ar, β), 128.1 (CH Ar, α), 128.0 (CH Ar, β), 127.7 (CH Ar), 67.8 (C4), 67.6 (*C*H$_2$Ar, α), 67.3 (*C*H$_2$Ar, β), 65.1 (C5, α), 65.0 (C5, β), 64.2 (CH_2OH), 46.4 (C3, α), 46.3 (C3, β), 36.1 (C1, β), 35.1 (C1, α), 27.7 (C7, α), 27.2 (C7, β), 22.5 (C6, α), 22.0 (C6, β).

Anal. Calcd for $C_{15}H_{19}NO_5$ (293.32): C, 61.4; H, 6.5. Found: C, 61.7; H, 6.2.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589109.

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