

Synthesis of Novel, Chiral Bicyclo[3.1.0]hex-2-ene Amino Acid Derivatives as Useful Synthons in Medicinal Chemistry

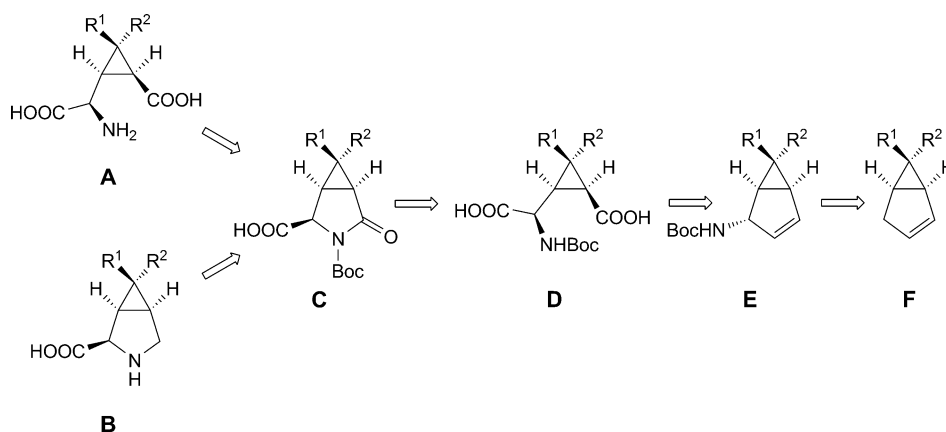
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A short and concise synthesis of novel, chiral bicyclo[3.1.0]hex-2-ene amino acid derivatives **13** and **14** has been developed. The key step is a stereo- and regioselective allylic amination of *exo*- and *endo*-methyl bicyclo[3.1.0]hex-2-ene-6-carboxylates **8** and **9**, which were prepared from 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one (**1**). These amino acid derivatives are useful building blocks in medicinal chemistry and can be prepared as chiral compounds by using either (+)-**1** or (–)-**1** as starting material.

1. Introduction. – Conformationally restricted α -amino acids **A** and **B** (*Scheme 1*) are useful tools for synthetic and medicinal chemists for the preparation of peptidomimetics, biologically active compounds, natural products, and organocatalysts [1]. (2-Carboxycyclopropyl)glycines **A** are of interest primarily as conformationally restricted analogs of glutamic acid, the major excitatory neurotransmitter in the central nervous system [2]. Proper choice of stereochemistry places the desired functional groups in such a way that the conformation of glutamate is fixed either in an extended or folded form [3], which allows the assessment of the spatial requirements for a wide range of ionotropic- (iGluRs) and metabotropic-glutamate receptors (mGluRs) [4], as well as different classes of transporters [5]. For example, **A** ($R^1 = \text{H}$, $R^2 = \text{COOH}$),

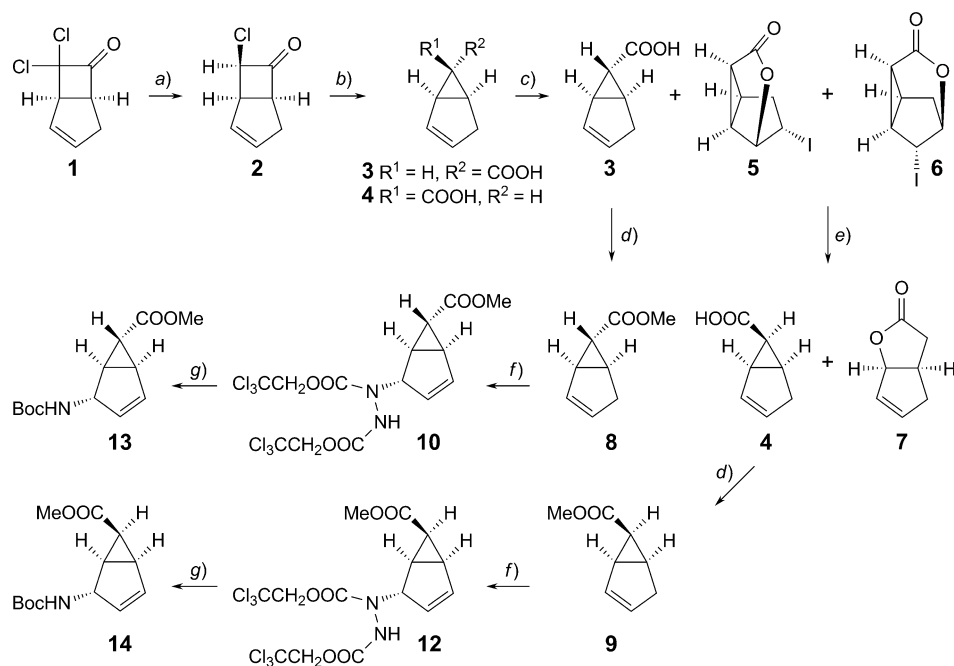
Scheme 1



DCG-IV) [6] is a potent mGluR₂ agonist, **A** (R¹ = H, R² = MeOCH₂, *trans*-MCG-IV) is a kainic acid agonist (iGluR), and **A** (R¹ = MeOCH₂, R² = H, *cis*-MCG-IV) is an *N*-methyl-D-aspartic agonist (iGluR) [7]. Proline derivatives **B** (R² or R¹ = COOMe) are members of the bicyclic amino acid family [8]. More specifically, they are a sub-class of proline-glutamic acid chimeras [9], in which backbone flexibility is restricted by the proline, and the conformation of the glutamate side chain is also locked, making them interesting building blocks for peptide synthesis [10]. Common precursors for the synthesis of **A** and **B** are the pyroglutamic acid derivatives **C** (R¹ = H, R² = COOMe; R¹ = COOMe, R² = H) [11], which by themselves are unique chiral synthons offering a wide variety of possible synthetic transformations [12]. Building block **C** (R¹ = H, R² = COOMe), synthesized from *Garner's* aldehyde [13] in some 20 steps, is an intermediate in the first synthesis of DCG-IV (**17**) by *Ohfuné* [6a] and is formed as a result of a spontaneous lactamization of the corresponding dicarboxylic amino acid **D**. To shorten the synthesis of the important building block **C**, we thought it should be possible to synthesize **D** from an amino substituted bicyclo[3.1.0]hex-2-ene derivative **E** by oxidative cleavage of the C=C bond. The γ -amino acid derivatives **E** (R¹ = H, R² = COOMe; R¹ = COOMe, R² = H) are conformationally restricted γ -amino butyric acid (GABA) analogs [14]. γ -Amino butyric acid, like glutamic acid, is present in the central nervous system [15], but in contrast to the latter, it acts through different receptors and transporters and functions as the major inhibitory neurotransmitter [16]. For the synthesis of building block **E**, we envisioned an allylic amination of methyl bicyclo[3.1.0]hex-2-en-6-carboxylates **F** as a possible route. In addition, these building blocks are interesting due to their relatively high level of saturation (Fsp³) and number of stereogenic centers [17], making them attractive novel synthons in medicinal chemistry [18]. Herein, we report the synthesis of building blocks **E** (R¹ = COOMe, R² = H; R¹ = H, R² = COOMe) in racemic and optically active form, their conversions into pyroglutamate derivatives **C**, and the preparation of (2-carboxycyclopropyl)glycines **A**.

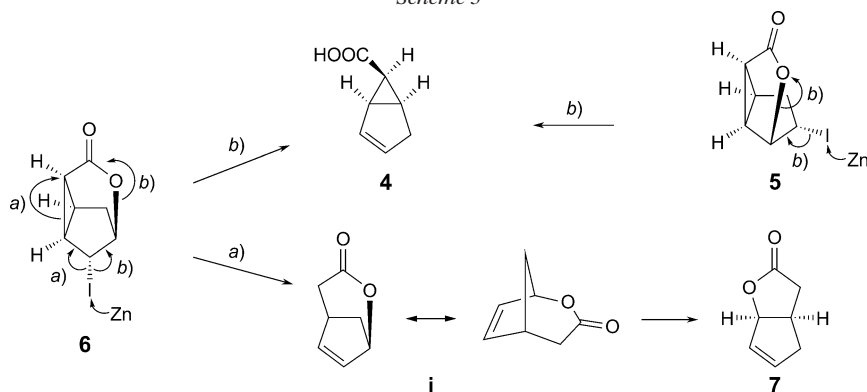
2. Results and Discussion. – 2.1. *Syntheses of exo- and endo-Methyl Bicyclo[3.1.0]-hex-2-ene-6-carboxylates 8 and 9.* From the known syntheses of *exo*- and *endo*-bicyclo[3.1.0.]carboxylic acids **3** and **4** [19], we decided to follow the route described by *Brook et al.* [19c], because the starting material 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one (**1**) is readily available in both enantiomeric forms [20], making the synthesis of our building blocks in homochiral form straightforward. To test and possibly refine our synthetic plan (*Scheme 2*), we first used commercially available racemic 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one (**1**) as the starting material. Reduction with Zn in AcOH and distillation afforded the reported *endo*-chloroketone **2** [21], which then underwent a *Favorski* ring contraction upon treatment with KOH in dioxane/H₂O to produce a 6:4 mixture of *exo*- and *endo*-acid **3** and **4**, which were separated *via* iodolactonization [19a] [19c]. Thus, treatment of this mixture with I₂/KI under basic conditions delivered γ -iodolactone **5** together with δ -iodolactone **6** in a ratio of 3:7 and *exo*-acid **3** [19a]. Subsequent treatment of these iodolactones with Zn under acidic conditions delivered not only the expected and already described *endo*-acid **4** (64%) [19a], but also a bicyclic lactone **7** (25%), which was identified by comparison of the ¹H- and ¹³C-NMR, and IR spectra with those described in [22]. We hypothesized (*Scheme 3*) that the undesired

Scheme 2



a) Zn, AcOH [21]. b) KOH, Dioxane/H₂O [19c]. c) I₂, KI, NaHCO₃ [19a]. d) 2,2-Dimethoxypropane, TsOH, MeOH [24]. e) Zn, AcOH, THF [19a]. f) BTCEAD, ClCH₂CH₂Cl, 85°. g) Zn, AcOH, acetone, then MeOH, Et₃N, (Boc)₂O.

Scheme 3

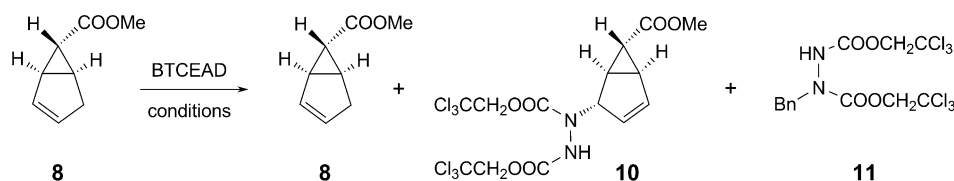


(in our case) bicyclic lactone **7** stems from the δ -lactone **6**, since formation of a C=C bond and opening of the three-membered ring (*Path a*) is not possible from the γ -lactone **5**, whereas formation of a C=C bond and liberation of the *endo*-acid **4** (*Path b*)

is possible from both lactones. The so-formed bridged lactone **i** is not stable under these conditions and rearranges readily to lactone **7** [23]. To test this hypothesis, we separated the γ -iodolactone **5** from the δ -iodolactone **6** by column chromatography and subjected each iodolactone individually to the Zn reduction conditions. Indeed, whereas a mixture of *endo*-acid **4** (61%) and bicyclic lactone **7** (31%) was obtained when starting with **6**, only *endo*-acid **4** (86%) was formed using **5** as starting material. Esterification [24] of these two acids afforded then *exo*-ester **8** (81%) [25] and *endo*-ester **9** (93%) [26], respectively.

2.2. Allylic Amination. With *exo*- and *endo*-ester **8** and **9** in hand, we turned our attention to the allylic amination [27]. Of particular concern was the level of regio- and stereoselectivity, which we might achieve in this process. Since our synthesis plan called for a *trans* relationship between the newly introduced N-function and the three-membered ring and complete control of the regiochemistry (to avoid any racemization in the chiral series), we selected the method reported by *Leblanc et al.* [28], namely an allylic amination of olefins with bis(2,2,2-trichloroethyl) azodicarboxylate (BTCEAD). Since the aza-ene reaction with olefins is thought to be a concerted, suprafacial process [29], and attack of the azodicarboxylate should occur from the less hindered side, we were confident of achieving the desired stereo- and regioselectivity. An additional advantage of that protocol are the mild conditions (Zn, AcOH, acetone) needed for the cleavage of the hydrazine to the amine. Besides the original procedure [28], which calls for running the reaction in benzene at different temperatures, two more variations are described in the literature: *i*) using different *Lewis* acids as catalysts in CH_2Cl_2 at room temperature [30], and *ii*) running the reaction ‘on water’ [31]. To find the best conditions for our case, we performed a short optimization with **8**, which is summarized in *Table 1*.

Table 1. Allylic Amination



BTCEAD = Bis(2,2,2-trichloroethyl) azodicarboxylate

Entry	Solvent	Catalyst	Temp.	Time [h]	Yield [%] ^{a)}		
					8	10	11
1	Benzene	none	80°	16	11	77	–
2	Toluene	none	110°	16	–	84	14
3	CH_2Cl_2	none	r.t.	48	43	50	–
4	CH_2Cl_2	$(\text{TfO})_2\text{Cu}$	r.t.	48	19	40	–
5	$\text{ClCH}_2\text{CH}_2\text{Cl}$	none	85°	16	–	93	–
6	H_2O	none	50°	10	–	83	–

^{a)} Yield of isolated product.

Running the reaction in benzene for 16 h at reflux temperature (*Entry 1*) yielded **10** (77%) and starting material **8** (11%). Increasing the temperature to 110° by using toluene (*Entry 2*) drove the reaction to completion (84%), but **11** was formed as an additional product, which can be explained by an azo-ene reaction of toluene and BTCEAD. Comparing the results using the conditions of *Jorgenson et al.* [30] (*Entry 4*) vs. running the reaction in CH₂Cl₂ without catalyst at room temperature (*Entry 3*) led us to conclude not to use a *Lewis* acid as catalyst, but to use 1,2-dichloroethane as solvent and perform the reaction at 85° (*Entry 5*). We were pleased to see that the reaction was finished after 16 h and yielded **10** in 93% yield. To complete our small study, we also tested the protocol described by *Sharpless et al.* [31] (*Entry 6*). These conditions delivered **10** after 10 h in 83% yield. The drawback of this method was the formation of a white lump embedded with yellow particles, which contained not only **10** but also BTCEAD. To drive the reaction to completion, it was found necessary to break up this lump after 6 h and 8 h. Taking account of these findings, for the reaction of the *endo*-ester **9** with BTCEAD we also used 1,2-dichloroethane as solvent and employed a reaction temperature of 85°, which enabled **12** to be obtained in 79% yield after 16 h (*Scheme 1*). To obtain an orthogonally protected building block, the last step of the protocol in [28] was modified slightly. Instead of protecting the amine, which is released after reductive treatment (Zn, AcOH, acetone), as an acetate, we employed (t-Boc)₂O as an acylating reagent to afford Boc-protected **13** (74%) and **14** (80%), respectively. The expected *trans* relationship between H–C(4) and H–C(5) could not be unequivocally confirmed, since the coupling constant between these two H-atoms in the ¹H-NMR spectrum could not easily be determined. Although the width at half maximum of the corresponding signals indicated that the coupling constant values were rather small, suggesting a *trans* relationship as evidenced in [32], the final proof of the configuration stemmed from the preparation of *rac*-DCG-IV (**17**; *Scheme 4*). Improved *Sharpless* conditions [33] applied to **13** and **14** delivered pyroglutamate derivatives **15** (88%) and **16** (82%) after spontaneous lactamization [6a] of the initially formed dicarboxylic amino acid [34]. The ¹H-NMR coupling constants $J(\text{H-C}(2), \text{H-C}(1)) = 6.0 \text{ Hz}$ in **15** and $J(\text{H-C}(2), \text{H-C}(1)) = 6.4 \text{ Hz}$ in **16** were in agreement with a *cis* relationship as reported in [35]. This, together with the conversion of **15** into *rac*-DCG-IV **17** (80%) [6] by acidic hydrolysis, corroborated the stereochemical outcome of the azo-ene reaction. Applying the same conditions to **16** produced, for the first time, the all *cis*-substituted cyclopropyl glycine derivative **18** in 84% yield (*Scheme 4*).

2.3. Chiral Series. For the synthesis of our chiral bicyclo[3.1.0]hex-2-ene building blocks, we modified our strategy in such a way that we decided not to separate the *endo*-acid **4** from the *exo*-acid **3** via iodolactonization, but to carry the mixture through the esterification and allylic amination steps and then isolate **13** and **14** as enantiomerically pure compounds by column chromatography. The results, using either (1*S*,5*R*)-7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one ((–)-**1**) [20] or the enantiomer (+)-**12** [20] as starting material, are shown in Table 2. The absolute configurations of these building blocks were initially deduced by assuming that the azo-ene reaction proceeds through a [$\pi 2_s + \pi 2_s + \sigma 2_s$] process according to the *Woodward–Hoffmann* notation [36]. The absolute configurations were subsequently confirmed by the synthesis of (2*R*,2'*S*,3'*S*)-2-(2',3'-dicarboxylcyclopropyl)glycine (*ent*-DCG IV) ((+)-**17**) [α]_D = +22.3, (–)-**17** [α]_D = –20.2 [6a]) from (+)-**13** by the reactions outlined above (*Scheme 4*).

Scheme 4

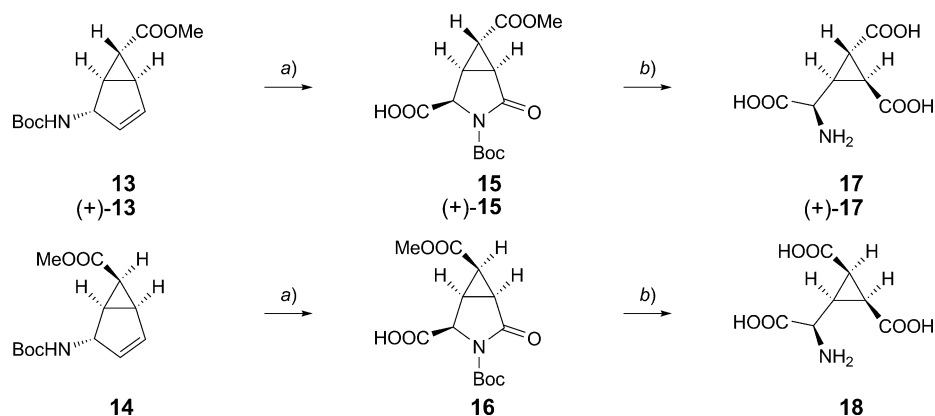
a) NaIO₄, RuCl₃, MeCN, CCl₄, H₂O. b) 10% HCl.

Table 2. Chiral Building Blocks

	(-)-1	(-)-13	(-)-14
[α] _D	-89.8 (-81.0 [20])	-195.7	-375.8
Configuration	(1S,5R) [20]	(1R,4R,5S,6S)	(1R,4R,5S,6R)
Chiral HPLC	n.d.	8.29 (-)	10.31 (-)
	(+)-1	(+)-13	(+)-14
[α] _D	+87.1 (+83.9 [20])	+181.5	+368.5
Configuration	(1R,5S) [20]	(1S,4S,5R,6R)	(1S,4S,5R,6S)
Chiral HPLC	n.d.	10.60 (+)	9.79 (+)

3. Conclusions. – In summary, we have developed a concise and fully stereo-controlled synthesis of the novel, chiral, bifunctional bicyclo[3.1.0]hex-2-ene building blocks **13** and **14**. These building blocks provide not only a short access to (2,3-dicarboxycyclopropyl)glycines **17** and **18**, but should also allow straightforward modification of the substituents at the 2 or 3 position of the three-membered ring. Additionally, together with the highly functionalized pyroglutamate derivatives **15** and **16**, they might be versatile building blocks in medicinal chemistry due to their chirality and three-dimensional shape.

We thank the Analytical Departments of the *Roche Innovation Center Basel* for skillful measurement of NMR, IR, MS, ORD, and chiral HPLC data. The careful reading of the manuscript by Dr. *Roger Norcross* is gratefully acknowledged.

Experimental Part

General. All solvents and reagents were used from commercial sources without further purification or prepared as described in the literature. Thin-layer chromatography (TLC): *EMD* pre-coated silica gel 60 *F₂₅₄* glass plates; visualization with UV light (254 nm) or chemical detection ((NH_4)₂Ce(MoO₄)₃ soln. or KMnO₄ soln.). Flash chromatography (FC): silica gel 60 (*Merck*, 230–400 mesh), with the eluent mixtures given for the corresponding procedures. Enantiomeric purities: chiral HPLC with an *Ultimate 3000* coupled with a *Chiralizer* (*IBZ Messtechnik*). Optical rotations (ORD): *Anton Parr MCP 500* at 20°. M.p.: *Büchi B-540* instrument; uncorrected. FT-IR (solid state (ATR)): *Nicolet iS5* instrument; $\tilde{\nu}$ in cm^{-1} . ¹H- and ¹³C-NMR spectra: *Bruker Avance II 300* or a *Bruker Avance III 600* spectrometer, in CDCl₃, (D₆)DMSO or D₂O; δ in ppm rel. to Me₄Si as internal standard, *J* in Hz. MS: *Applied Biosystem API300*; in *m/z*. HR-LC/MS: *Agilent Q-TOF 6520* system; in *m/z*. Elemental analyses: *Solvias AG* (Mattenstrasse, Postfach, CH-4002 Basel, Switzerland).

(*IRS,5SR,6SR*)-*Bicyclo[3.1.0]hex-2-ene-6-carboxylic Acid* (**4**) and (*3aRS,6aSR*)-*3,3a,4,6a-Tetrahydro-2H-cyclopenta[b]furan-2-one* (**7**). To a soln. of a mixture (3:7) of iodolactones **5** and **6** [19a][19c] (7.50 g, 30 mmol) in THF (50 ml), AcOH (1.5 ml), and H₂O (1.5 ml) was added Zn (3.3 g, 58.5 mmol) in small portions at 0° (ice/water bath). Then, the ice/water bath was removed, and the mixture was stirred for 1.5 h at ambient temp. After filtration through a pad of *Celite*, the filtrate was partially concentrated, diluted with H₂O (75 ml), and acidified with 25% HCl to pH = 1. The aq. layer was extracted with Et₂O (3 × 80 ml). The combined org. extracts were dried (Na₂SO₄) and concentrated to give 3.48 g of crude product, which was purified by FC (heptane/AcOEt 4:1) to give **7** (0.94 g, 25%) as colorless oil (IR, ¹H- and ¹³C-NMR spectra as described in [22]) and **4** (2.41 g, 64%) as colorless solid. M.p. 88–91° (90–91° [19a]).

Separation of exo-8-Iodo-2-oxatricyclo[3.3.0.0^{4,6}]octan-3-one (**5**) and *exo-6-Iodo-4-oxatricyclo[3.2.1.0^{2,7}]octan-3-one* (**6**). A mixture of the iodolactones **5** and **6** (4.81 g, 19.2 mmol) was separated by FC (heptane/AcOEt 4:1) to afford **5** (1.25 g; *R_f* (heptane/AcOEt 4:1) 0.37) and **6** (3.38 g; *R_f* (heptane/AcOEt 4:1) 0.24).

Data of 5. M.p. 120.6–121.4° (cyclohexane). IR (ATR): 2914w, 2857w, 1758s, 1440m, 1360m, 1342m, 1320s, 1301m, 1276m, 1258w, 1209m, 1194m, 1030s, 1045m, 1005s, 991s, 964s, 920s, 897m, 868m, 824s, 798s, 783m, 667m, 619m, 591s. ¹H-NMR (600 MHz, CDCl₃): 5.08 (br. d, *J* = 4.2, H–C(1)); 4.29 (br. d, *J* = 4.7, H–C(8)); 3.37 (td, *J* = 6.1, 4.2, H–C(5)); 2.69 (ddd, *J* = 16.3, 6.4, 1.4, H–C(7)); 2.52 (ddd, *J* = 16.3, 4.7, 1.6, H–C(7)); 2.31 (ddd, *J* = 8.4, 6.1, 1.5, H–C(4)); 2.22 (ddd, *J* = 8.4, 6.1, 1.6, H–C(6)). ¹³C-NMR (75 MHz, CDCl₃): 174.1 (C(3)); 87.9 (C(1)); 35.8, 34.4, 34.0 (C(5,7,8)); 29.2 (C(4)); 27.1 (C(6)). GC/EI-MS: 250 (*M*⁺), 123 ([*M* – I]⁺), 79 ([*M* – I – CO₂]⁺). Anal. calc. for C₇H₇IO₂ (250.03): C 33.63, H 2.82, I 50.75; found C 33.48, H 2.96, I 50.67.

Data of 6. M.p. 114.6–115.1° (cyclohexane). IR (ATR): 2978w, 2949w, 2858w, 1723s, 1711s, 1436w, 1374m, 1354m, 1329m, 1318w, 1275w, 1254w, 1210s, 1183w, 1160m, 1147m, 1096m, 1085m, 1025s, 987s, 967s, 952s, 924m, 886m, 854m, 838m, 809s, 783m, 762m, 713m, 649m, 598s. ¹H-NMR (600 MHz, CDCl₃): 4.69–4.67 (m, H–C(5)); 4.14 (br. s, H–C(6)); 2.68 (dt, *J* = 13.7, 3.0, H–C(8)); 2.56–2.53 (m, H–C(7)); 2.32–2.28 (m, H–C(1)); 2.00 (td, *J* = 7.5, 0.8, H–C(2)); 1.93 (dd, *J* = 17.7, 0.7, H–C(8)). ¹³C-NMR (75 MHz, CDCl₃): 168.3 (C(3)); 79.0 (C(5)); 27.7, 26.6 (C(1,7)); 25.6 (C(2)); 21.6, 20.1 (C(6,8)). GC/EI-MS: 250 (*M*⁺), 123 ([*M* – I]⁺), 79 ([*M* – I – CO₂]⁺). Anal. calc. for C₇H₇IO₂ (250.03): C 33.63, H 2.82, I 50.75; found C 33.57, H 2.97, I 50.55.

(*IRS,5SR,6SR*)-*Bicyclo[3.1.0]hex-2-ene-6-carboxylic Acid* (**4**) and (*3aRS,6aSR*)-*3,3a,4,6a-Tetrahydro-2H-cyclopenta[b]furan-2-one* (**7**). To a soln. of δ -iodolactone **6** (2.50 g, 10 mmol) in THF (16 ml), AcOH (0.5 ml), and H₂O (0.5 ml) was added Zn (1.1 g, 19.5 mmol) in small portions at 0° (ice/water bath). Then, the ice/water bath was removed, and the mixture was stirred for 1.5 h at ambient temp. After filtration through a pad of *Celite*, the filtrate was partially concentrated, diluted with H₂O (25 ml), and

acidified with 25% HCl to pH = 1. The aq. layer was extracted with Et₂O (3 × 50 ml). The combined org. extracts were dried (Na₂SO₄) and concentrated to give 1.24 g of crude product, which was purified by FC (heptane/AcOEt 4:1) to give **7** (0.38 g, 31%) and **4** (0.76 g, 61%).

(*1RS,5SR,6SR*)-*Bicyclo[3.1.0]hex-2-ene-6-carboxylic Acid* (**4**). To a soln. of γ -iodolactone **5** (1.0 g, 4 mmol) in THF (10 ml), AcOH (0.3 ml), and H₂O (0.3 ml) was added Zn (0.51 g, 7.8 mmol) in small portions at 0° (ice/water bath). Then, the ice/water bath was removed, and the mixture was stirred for 1.5 h at ambient temp. After filtration through a pad of *Celite*, the filtrate was partially concentrated, diluted with H₂O (10 ml), and acidified with 25% HCl to pH = 1. The aq. layer was extracted with Et₂O (3 × 30 ml). The combined org. extracts were dried (Na₂SO₄) and concentrated to give **4** (0.43 g, 86%).

Methyl (1RS,5SR,6SR)-Bicyclo[3.1.0]hex-2-ene-6-carboxylate (**8**). To a soln. of **3** [19c] (8.69 g, 70 mmol) in MeOH (300 ml) and 2,2-dimethoxypropane (100 ml) was added TsOH (3.34 g, 17.6 mmol), and the mixture was stirred for 24 h at ambient temp. The soln. was partly concentrated, then H₂O (200 ml) and Et₂O (200 ml) were added. The layers were separated, and the aq. phase was extracted with Et₂O (2 × 200 ml). The combined org. layers were washed with 0.5N NaOH (200 ml), H₂O (200 ml), and brine (200 ml), then dried (Na₂SO₄), and evaporated to give light-yellow oil (8.61 g), which was distilled (Kugelrohr, 75–80°, 0.5 Torr) to yield **8** (7.98 g, 81%). ¹H-NMR Spectrum as described in [24].

Methyl (1RS,5SR,6SR)-Bicyclo[3.1.0]hex-2-ene-6-carboxylate (**9**). To a soln. of **4** (2.48 g, 20 mmol) in MeOH (100 ml) and 2,2-dimethoxypropane (30 ml) was added TsOH (0.95 g, 5 mmol), and the soln. was stirred for 24 h at 40°. The soln. was partly concentrated, then H₂O (120 ml) and Et₂O (120 ml) were added. The layers were separated, and the aq. phase was extracted with Et₂O (2 × 120 ml). The combined org. layers were washed with 0.5N NaOH (120 ml), H₂O (120 ml), and brine (120 ml), then dried (Na₂SO₄) and evaporated to give light-yellow oil (2.89 g), which was distilled (Kugelrohr, 75–80°, 0.5 Torr) to yield **9** (2.58 g, 93%). ¹H-NMR Spectrum as described in [25][26].

Bis(2,2,2-trichloroethyl) 1-[(1RS,2SR,5SR,6RS)-6-(Methoxycarbonyl)bicyclo[3.1.0]hex-3-en-2-yl]hydrazine-1,2-dicarboxylate (**10**). i) In benzene: A soln. of **8** (691 mg, 5 mmol) and bis(2,2,2-trichloroethyl) azodicarboxylate (2.28 g, 6 mmol) in benzene (25 ml) was heated for 16 h at 85° (oil bath). The soln. was concentrated, and the residue (2.64 g) was purified by FC (heptane/AcOEt 10:1) to yield **8** (78 mg, 11%) as colorless oil and **10** (2.01 g, 77%) as light-yellow foam.

Data of 10. IR (ATR): 3310s, 3080w, 3069w, 3062w, 3001m, 2925s, 2854s, 1768s, 1731s, 1704s, 1503m, 1445s, 1403s, 1365m, 1347w, 1289s, 1253s, 1201s, 1179s, 1144s, 1106m, 1082w, 1058m, 1044m, 1024w, 981w, 963w, 918w, 897w, 853m, 820s, 791s, 754s, 711s, 650m, 606w, 570s. ¹H-NMR (600 MHz, (D₆)DMSO, 120°): 9.65 (br. s, NH); 6.20 (br. d, *J* = 5.1, H–C(4')); 5.52–5.41 (*m*, H–C(3')); 5.09–5.07 (*m*, H–C(2')); 4.86 (*s*, CH₂O); 4.79 (br. s, CH₂O); 3.59 (*s*, MeO), 2.51–2.47, 2.45–2.38 (*2m*, H–C(1',5')); 1.03 (*t*, *J* = 2.9, H–C(6')). ESI-MS: 515 ([*M* – H][–]).

ii) In toluene: A soln. of **8** (691 mg, 5 mmol) and bis(2,2,2-trichloroethyl) azodicarboxylate (2.28 g, 6 mmol) in toluene (25 ml) was heated for 16 h at 110° (oil bath). The soln. was concentrated, and the residue (2.76 g) was purified by FC (heptane/AcOEt 4:1) to yield *bis*(2,2,2-trichloroethyl) 1-*benzylhydrazine-1,2-dicarboxylate* (**11**; 0.34 g, 14%) as light-yellow solid and **10** (2.18 g, 84%) as light-yellow foam.

Data of 11. ¹H-NMR (600 MHz, (D₆)DMSO, 120°): 9.88 (br. s, NH); 7.36–7.24 (*m*, 5 arom. H); 4.86, 4.78, 4.68 (3s, 2 × CH₂O, CH₂N). ESI-MS: 469 ([*M* – H][–]).

iii) In CH₂Cl₂: A soln. of **8** (691 mg, 5 mmol) and bis(2,2,2-trichloroethyl) azodicarboxylate (2.28 g, 6 mmol) in CH₂Cl₂ (25 ml) was stirred for 48 h at ambient temp. The soln. was concentrated, and the residue (2.86 g) was purified by FC (heptane/AcOEt 10:1) to yield **8** (298 mg, 43%) as colorless oil and **10** (1.31 g, 50%) as light-yellow foam.

iv) In CH₂Cl₂ with (TfO)₂Cu: To a soln. of **8** (691 mg, 5 mmol) and bis(2,2,2-trichloroethyl) azodicarboxylate (2.28 g, 6 mmol) in CH₂Cl₂ (25 ml) was added (TfO)₂Cu (362 mg, 1 mmol), and the mixture was stirred for 48 h at ambient temp. The soln. was concentrated, and the residue (3.12 g) was purified by FC (heptane/AcOEt 10:1) to yield **8** (132 mg, 19%) as colorless oil and **10** (1.06 g, 40%) as light-yellow foam.

v) In ClCH₂CH₂Cl: A soln. of **8** (691 mg, 5 mmol) and bis(2,2,2-trichloroethyl) azodicarboxylate (2.28 g, 6 mmol) in ClCH₂CH₂Cl (25 ml) was stirred for 16 h at 85° (oil bath). The soln. was concentrated,

and the residue (2.88 g) was purified by FC (heptane/AcOEt 10:1) to yield **10** (2.42 g, 93%) as light-yellow foam.

vi) 'On water': To a suspension of bis(2,2,2-trichloroethyl) azodicarboxylate (2.28 g, 6 mmol) in H₂O (25 ml) was added **8** (691 mg, 5 mmol), and the mixture was stirred for 6 h at 50° (oil bath). A light-yellow lump formed and was broken up, and the suspension was stirred for another 2 h. The same procedure was repeated, and the suspension was stirred for another 2 h. The mixture was cooled, and the suspension was extracted with AcOEt (2 × 80 ml). The combined org. layers were dried (Na₂SO₄) and evaporated to give 2.67 g of crude product, which was purified by FC (heptane/AcOEt 10:1) to yield **10** (2.16 g, 83%) as light-yellow foam.

Bis(2,2,2-trichloroethyl) 1-[(1RS,2SR,5SR,6SR)-6-(Methoxycarbonyl)bicyclo[3.1.0]hex-3-en-2-yl]hydrazine-1,2-dicarboxylate (12). A soln. of **9** (2.07 g, 15 mmol) and bis(2,2,2-trichloroethyl) azodicarboxylate (6.85 g, 18 mmol) in ClCH₂CH₂Cl (75 ml) was stirred for 16 h at 85° (oil bath). The soln. was concentrated, and the residue (7.37 g) was purified by FC (heptane/AcOEt 10:1) to yield **12** (6.21 g, 79%) as light-yellow foam. ¹H-NMR (600 MHz, (D₆)DMSO, 120°): 9.62 (br. s, NH); 5.89 (br. d, *J* = 5.5, H-C(4')); 5.56 (br. s, H-C(2')); 5.42–5.39 (*m*, H-C(3')); 4.86 (*s*, CH₂O); 4.79 (br. s, CH₂O); 3.50 (*s*, MeO); 2.47–2.45 (*m*, 1 H) and 2.21–2.18 (*m*, 2 H) (H-C(1',5',6')). ESI-MS: 515 ([*M* – H][–]).

Methyl (1RS,4RS,5SR,6SR)-4-[(tert-Butoxycarbonyl)amino]bicyclo[3.1.0]hex-2-ene-6-carboxylate (13). To a soln. of **10** (1.56 g, 3 mmol) in THF (13.5 ml), acetone (1.5 ml), and AcOH (3 ml) was added Zn (4.68 g, 71.5 mmol) in small portions over 30 min. After 2 h, the mixture was filtered, and the soln. was concentrated. MeOH (15 ml) and Et₃N (1.38 ml, 9.9 mmol) were added, and the soln. was cooled to 0°. After addition of (Boc)₂O (720 mg, 3.3 mmol), the mixture was stirred for 5 h at ambient temp. The soln. was concentrated, and the residue was dissolved in CH₂Cl₂ (50 ml). The org. phase was washed with sat. NH₄Cl soln. (2 × 35 ml) and H₂O (35 ml), dried (Na₂SO₄) and concentrated to give 689 mg of crude product, which was purified by FC (heptane/AcOEt 4:1) to give **13** (563 mg, 74%) as colorless oil, which solidified on standing. An anal. sample was recrystallized (AcOEt, hexane). *R*_f (heptane/AcOEt 4:1) 0.41. M.p. 79.9–80.5°. IR (ATR): 3355*m*, 3078*w*, 3055*w*, 2977*w*, 2933*w*, 1724*m*, 1680*s*, 1677*s*, 1505*m*, 1457*w*, 1435*m*, 1389*w*, 1366*m*, 1328*w*, 1321*w*, 1264*m*, 1254*m*, 1237*m*, 1172*s*, 1078*w*, 1046*m*, 1028*m*, 992*w*, 961*w*, 951*w*, 933*w*, 865*m*, 853*w*, 829*w*, 801*w*, 789*w*, 762*w*, 748*w*, 716*w*, 703*w*, 695*w*, 647*w*, 610*w*, 579*w*, 552*w*. ¹H-NMR (600 MHz, CDCl₃): 6.11 (*dddd*, *J* = 5.5, 2.2, 1.3, 0.7, H-C(2)); 5.50 (*ddd*, *J* = 5.5, 1.8, 1.6, H-C(3)); 4.64–4.51 (*m*, H-C(4)), NH); 3.66 (*s*, MeO); 2.46 (*dq*, *J* = 6, 2.2, H-C(1)); 2.30–2.25 (*m*, H-C(5)); 1.46 (*s*, Me₃C); 1.16 (br. *dd*, *J* = 3.2, 2.2, H-C(6)). ¹³C-NMR (150 MHz, CDCl₃): 171.6 (COOMe); 154.8 (NCOOC); 135.4 (C(2)); 130.2 (C(3)); 79.8 (NCOOC); 57.2 (C(4)); 51.8 (MeO); 33.5, 33.1, 32.1 (C(1,5,6)); 28.4 (Me₃C). ISP-MS: 270.9 ([*M* + NH₄]⁺), 254.0 ([*M* + H]⁺). Anal. calc. for C₁₃H₁₉NO₄ (253.30): C 61.64, H 7.56, N 5.53; found C 61.66, H 7.50, N 5.55. Chiral HPLC (*Reprosil Chiral-NR*): heptane/EtOH 90:10, flow rate 1 ml/min, *t*_R 8.00 min (–), *t*_R 10.40 min (+).

Methyl (1RS,4RS,5SR,6RS)-4-[(tert-Butoxycarbonyl)amino]bicyclo[3.1.0]hex-2-ene-6-carboxylate (14). To a soln. of **12** (5.19 g, 10 mmol) in THF (45 ml), acetone (5 ml), and AcOH (10 ml) was added Zn (15.6 g, 23.9 mmol) in small portions over 45 min. After 6 h, the mixture was filtered, and the soln. was concentrated. MeOH (50 ml) and Et₃N (4.6 ml, 33 mmol) were added, and the soln. was cooled to 0°. After addition of (Boc)₂O (2.40 g, 11 mmol), the mixture was stirred for 5 h at ambient temp. The soln. was concentrated, and the residue was dissolved in CH₂Cl₂ (200 ml). The org. phase was washed with sat. NH₄Cl soln. (2 × 150 ml) and H₂O (150 ml), dried (Na₂SO₄) and concentrated to give 2.46 g of crude product, which was purified by FC (heptane/AcOEt 4:1) to give **14** (2.05 mg, 80%) as colorless oil, which solidified on standing. An anal. sample was recrystallized (AcOEt, hexane). *R*_f (AcOEt/heptane 1:4) 0.24. M.p. 98.5–99.0°. IR (ATR): 3323*w*, 2980*w*, 2928*w*, 1724*s*, 1689*s*, 1521*s*, 1438*m*, 1386*w*, 1365*m*, 1300*s*, 1275*w*, 1263*m*, 1244*w*, 1206*w*, 1164*s*, 1148*s*, 1219*s*, 1084*m*, 1061*m*, 1041*m*, 1023*m*, 973*m*, 962*m*, 938*w*, 885*m*, 866*w*, 824*w*, 812*w*, 793*w*, 768*w*, 746*m*, 663*m*. ¹H-NMR (600 MHz, CDCl₃): 5.84 (br. *d*, *J* = 5.5, H-C(2)); 5.68 (*ddd*, *J* = 5.5, 1.8, 0.6, H-C(3)); 4.93 (br. *d*, *J* = 7.6, H-C(4)); 4.51 (br. *d*, *J* = 7.6, NH); 3.58 (*s*, MeO), 2.45 (*ddt*, *J* = 8, 5.6, 2.4, H-C(1)); 2.08 (*ddd*, *J* = 8.0, 0.7, 0.6, H-C(6)); 1.98 (br. *dd*, *J* = 8.0, 5.6, H-C(5)); 1.46 (*s*, Me₃C). ¹³C-NMR (75 MHz, CDCl₃): 169.2 (COOMe); 154.8 (NCOOC); 132.3, 130.6 (C(2,3)); 79.6 (Me₃C); 55.1 (CN); 51.5 (MeO); 30.3, 29.6, 28.7 (C(1,5,6)); 28.4 (Me₃C). ISP-MS: 270.1 ([*M* + NH₄]⁺), 254.1 ([*M* + H]⁺). Anal. calc. for C₁₃H₁₉NO₄ (253.30): C 61.64, H 7.56, N 5.53; found C 61.41,

H 7.25, N 5.44. Chiral HPLC (*Reprosil Chiral-NR*): heptane/EtOH 90:10, flow rate 1 ml/min, t_R 10.00 min (+), t_R 10.49 min (–).

(*1R,2RS,5SR,6SR*)-3-(*tert*-Butoxycarbonyl)-6-(methoxycarbonyl)-4-oxo-3-azabicyclo[3.1.0]hexane-2-carboxylic Acid (**15**). To a soln. of **13** (1.01 g, 4 mmol) in a mixture of MeCN (12 ml), CCl₄ (12 ml), and H₂O (18 ml) was added NaIO₄ (3.51 g, 16.4 mmol) followed by RuCl₃ (18.3 mg, 0.088 mmol) at ambient temp. After stirring for 4 h, the mixture was diluted with CH₂Cl₂ (25 ml) and H₂O (10 ml). The phases were separated, and the aq. phase was extracted with CH₂Cl₂ (2 × 20 ml). The combined org. extracts were dried (Na₂SO₄) and concentrated to give 1.06 g of light-red foam, which was purified by FC (AcOEt/AcOH 95:5) to give **15** (1.0 g, 88%) as white foam. An anal. sample was crystallized from AcOEt. M.p. 126.5–127.3°. IR (ATR): 3457w, 3188w (br.), 3086w, 2923s, 2853s, 2728w, 2614w, 1788s, 1730s, 1497w, 1396w, 1373w, 1306m, 1256m, 1150m, 1086m, 1058m, 1016m, 945w, 906w, 879w, 846w, 814w, 763w, 738w, 673w, 618w, 585w. ¹H-NMR (600 MHz, CDCl₃): 6.75 (br. s, COOH); 4.81 (d, J = 6.0, H–C(2)); 3.72 (s, MeO); 2.70 (ddd, J = 6.6, 6.0, 2.8, H–C(1)); 2.59 (dd, J = 6.6, 2.8, H–C(5)); 2.40 (t, J = 2.8, H–C(6)); 1.47 (s, Me₃C). ¹³C-NMR (150 MHz, CDCl₃): 172.9, 169.6, 169.0 (C(4), COOMe, COOH); 148.9 (NCO); 84.6 (Me₃C), 58.2 (C(2)); 52.7 (MeO); 29.3 (C(5)); 27.6 (Me₃C); 22.0, 21.9 (C(1,6)). ISP-MS: 301.4 ([M + H]⁺). Anal. calc. for C₁₃H₁₇NO₇ (299.28): C 52.17, H 5.73, N 4.68; found C 51.74, H 5.76, N 4.63.

(*1R,2RS,5SR,6RS*)-3-(*tert*-Butoxycarbonyl)-6-(methoxycarbonyl)-4-oxo-3-azabicyclo[3.1.0]hexane-2-carboxylic Acid (**16**). To a soln. of **14** (507 mg, 2 mmol) in a mixture of MeCN (6 ml), CCl₄ (6 ml), and H₂O (9 ml) was added NaIO₄ (1.75 g, 8.2 mmol), followed by RuCl₃ (9.92 mg, 0.044 mmol) at ambient temp. After stirring for 4 h, the mixture was diluted with CH₂Cl₂ (15 ml) and H₂O (5 ml). The phases were separated, and the aq. phase was extracted with CH₂Cl₂ (2 × 15 ml). The combined org. extracts were dried (Na₂SO₄) and concentrated to give 581 mg of light-red foam, which was separated by FC (AcOEt/AcOH 95:5) to yield **16** as white foam (491 mg, 82%). An anal. sample was crystallized from AcOEt. M.p. 144.1–146.2°. IR (ATR): 3276w (br.), 2967w, 1780s, 1752s, 1731m, 1685m, 1476w, 1435w, 1395w, 1369w, 1350m, 1336m, 1314m, 1301m, 1254w, 1211s, 1151s, 1093w, 1076m, 1054w, 1016m, 984m, 957m, 944s, 918w, 869w, 854m, 835w, 824m, 779m, 763w, 734w, 694m. ¹H-NMR (600 MHz, CDCl₃): 4.92 (d, J = 6.4, H–C(2)); 3.71 (s, MeO); 2.74 (br. s, COOH); 2.59 (dt, J = 8.6, 6.4, H–C(1)); 2.53 (dd, J = 8.6, 6.4, H–C(5)); 2.25 (t, J = 8.6, H–C(6)); 1.49 (s, Me₃C). ¹³C-NMR (75 MHz, CDCl₃/(D₆)DMSO (1 drop)): 169.2, 169.0, 167.0 (C(4), COOMe, COOH); 147.9 (NCO); 82.5 (Me₃C); 57.5 (C(2)); 51.7 (MeO); 27.3 (Me₃C); 26.0, 24.7 (C(5,6)); 21.4 (C(1)). ISP-MS: 300.11 ([M + H]⁺). Anal. calc. for C₁₃H₁₇NO₇ (299.28): C 52.17, H 5.73, N 4.68; found C 51.79, H 5.61, N 4.60.

(*1R,2RS*)-3-[(*SR*)-Amino(carboxy)methyl]cyclopropane-1,2-dicarboxylic Acid (**17**). A soln. of **15** (299 mg, 1 mmol) in 10% HCl (10 ml) was heated at 100° (oil bath) for 3 h. The soln. was cooled to r.t. and concentrated to give 281 mg of crude product, which was submitted to ion exchange chromatography (Dowex 50WX4, elution with 12.5% NH₃·H₂O) to give **17** (205 mg, 86%) as white, hygroscopic foam (diammonium salt). ¹H-NMR (600 MHz, D₂O): 3.95 (d, J = 9.9, H–C(2)); 2.09 (dd, J = 9.5, 5.0, H–C(3)); 1.98 (dd, J = 5.6, 5.0, H–C(2)); 1.83 (ddd, J = 9.9, 9.5, 5.6, H–C(1)). ¹³C-NMR (150 MHz, D₂O): 178.8, 177.1, 173.5 (3 CO); 52.2 (C(2)); 29.5, 28.4, 26.9 (C(1,2,3)). LC/HR-MS: 203.0439 (C₇H₉NO₆⁺; calc. 203.0429).

(*1R,2SR,3rs*)-3-[(*RS*)-Amino(carboxy)methyl]cyclopropane-1,2-dicarboxylic Acid (**18**). A soln. of **16** (213 mg, 0.71 mmol) in 10% HCl (8 ml) was heated at 100° (oil bath) for 3 h. The soln. was cooled to r.t. and concentrated to give 253 mg of crude product, which was submitted to ion exchange chromatography (Dowex 50WX4, elution with 12.5% NH₃·H₂O) to give **18** (143 mg, 84%) as white, hygroscopic foam (diammonium salt). ¹H-NMR (600 MHz, D₂O): 4.44 (d, J = 10.9, H–C(2)); 2.17–2.08 (m, H–C(1,2)); 1.64 (dt, J = 10.9, 8.7, H–C(3)). ¹³C-NMR (150 MHz, D₂O): 176.1, 175.8, 174.6 (3 CO), 51.1 (C(2)), 29.5, 28.4, 26.9 (C(1,2,3)). LC/HR-MS: 203.0448 (C₇H₉NO₆⁺; calc. 203.0429).

Methyl (*1R,4R,5S,6S*)-4-[(*tert*-Butoxycarbonyl)amino]bicyclo[3.1.0]hex-2-ene-6-carboxylate ((–)-**13**) and Methyl (*1R,4R,5S,6R*)-4-[(*tert*-Butoxycarbonyl)amino]bicyclo[3.1.0]hex-2-ene-6-carboxylate ((–)-**14**). To a soln. of (*1S,5R*)-7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one ((–)-**1**; 4.43 g, 25 mmol; [α]_D = –89.8 (c = 1 in CHCl₃) ([α]_D = –81.0 (c = 0.75 in CHCl₃) [20]) in AcOH (125 ml) was added with stirring and cooling Zn (1.64 g, 25 mmol) in small portions over a period of 30 min. The soln. was diluted with H₂O (150 ml) and extracted with AcOEt (3 × 120 ml). The org. layer was washed with H₂O

(200 ml), sat. NaHCO₃ soln. (2 × 200 ml), dried (Na₂SO₄), and concentrated to give a mixture (92 : 8) of (1*S*,5*R*,7*S*)-7-chlorobicyclo[3.2.0]hept-2-en-6-one and (1*S*,5*R*,7*R*)-7-chlorobicyclo[3.2.0]hept-2-en-6-one (3.56 g, 97%) as light-yellow oil, which was used for the next step without further purification.

A mixture (92 : 8) of (1*S*,5*R*,7*S*)-7-chlorobicyclo[3.2.0]hept-2-en-6-one and (1*S*,5*R*,7*R*)-7-chlorobicyclo[3.2.0]hept-2-en-6-one (3.46 g, 24.3 mmol) was added dropwise to a soln. of KOH (9.53 g, 170 mmol) in a mixture of H₂O (105 ml) and dioxane (45 ml) at ambient temp. After 30 min, the soln. was acidified to pH = 1 with 25% HCl. The aq. phase was extracted with CH₂Cl₂ (3 × 100 ml), dried (Na₂SO₄), and concentrated to give a 3 : 1 mixture (H–C(2) signal in ¹H-NMR spectrum) of (1*S*,5*R*,6*S*)-bicyclo[3.1.0]hex-2-ene-6-carboxylate and (1*S*,5*R*,6*R*)-bicyclo[3.1.0]hex-2-ene-6-carboxylate (2.85 g, 94%) as white solid, which was used directly for the next step.

To a soln. of a mixture (3 : 1) of (1*S*,5*R*,6*S*)-bicyclo[3.1.0]hex-2-ene-6-carboxylate and (1*S*,5*R*,6*R*)-bicyclo[3.1.0]hex-2-ene-6-carboxylate (2.85 g, 23 mmol) in MeOH (100 ml) and 2,2-dimethoxypropane (35 ml) was added TsOH (1.09 g, 5.74 mmol), and the soln. was stirred for 24 h at 40°. The soln. was partly concentrated, then H₂O (80 ml) and Et₂O (80 ml) were added. The layers were separated, and the aq. phase was extracted with Et₂O (80 ml). The combined org. layers were washed with 0.5*N* NaOH (80 ml), H₂O (80 ml), and brine (80 ml), dried (Na₂SO₄), and evaporated to give light-yellow oil (2.84 g), which was distilled (Kugelrohr, 75–80°, 0.5 Torr) to yield a 3 : 1 mixture (MeO signal in ¹H-NMR-spectrum) of methyl (1*S*,5*R*,6*S*)-bicyclo[3.1.0]hex-2-ene-6-carboxylate and methyl (1*S*,5*R*,6*R*)-bicyclo[3.1.0]hex-2-ene-6-carboxylate as colorless oil (2.41 g, 76%).

A soln. of methyl (1*S*,5*R*,6*S*)-bicyclo[3.1.0]hex-2-ene-6-carboxylate and methyl (1*S*,5*R*,6*R*)-bicyclo[3.1.0]hex-2-ene-6-carboxylate (3 : 1) (2.07 g, 15 mmol) and bis(2,2,2-trichloroethyl) azodicarboxylate (6.85 g, 18 mmol) in ClCH₂CH₂Cl (75 ml) was stirred at 85° (oil bath) for 16 h. The mixture was concentrated, and the residue was purified by FC (heptane/AcOEt 4 : 1) to give bis(2,2,2-trichloroethyl) 1-[(1*S*,2*R*,5*R*,6*S*)-6-(methoxycarbonyl)bicyclo[3.1.0]hex-3-en-2-yl]hydrazine-1,2-dicarboxylate and bis(2,2,2-trichloroethyl) 1-[(1*S*,2*R*,5*R*,6*R*)-6-(methoxycarbonyl)bicyclo[3.1.0]hex-3-en-2-yl]hydrazine-1,2-dicarboxylate (6.18 g, 79%; 3 : 1) as colorless foam.

To a soln. of bis(2,2,2-trichloroethyl) 1-[(1*S*,2*R*,5*R*,6*S*)-6-(methoxycarbonyl)bicyclo[3.1.0]hex-3-en-2-yl]hydrazine-1,2-dicarboxylate and bis(2,2,2-trichloroethyl) 1-[(1*S*,2*R*,5*R*,6*R*)-6-(methoxycarbonyl)bicyclo[3.1.0]hex-3-en-2-yl]hydrazine-1,2-dicarboxylate (3 : 1 mixture) (3.11 g, 6 mmol) in THF (27 ml), acetone (3 ml) and AcOH (6 ml) was added Zn (9.33 g, 143 mmol) in small portions over 30 min. After 5 h, the mixture was filtered, and the soln. was concentrated. MeOH (30 ml) and Et₃N (2.76 ml, 19.8 mmol) were added, and the soln. was cooled to 0°. After addition of (t-Boc)₂O (1.44 g, 6.6 mmol), the mixture was stirred for 5 h at ambient temp. The soln. was concentrated, and the residue was dissolved in CH₂Cl₂. The org. phase was washed with sat. NH₄Cl soln. (2 × 60 ml) and H₂O (60 ml), dried (Na₂SO₄), and concentrated to give 1.29 g of crude product, which was purified by FC (heptane/AcOEt 4 : 1) and crystallized (AcOEt, hexane) to give (–)-**13** (0.89 g, 59%) as colorless needles, *R*_f (heptane/AcOEt 4 : 1) 0.39. ¹H-NMR spectrum identical to **13**. M.p. 84.4–85.1°, [*α*]_D = –195.7 (*c* = 1 in CHCl₃), chiral HPLC (*Reprosil Chiral-NR*): heptane/EtOH 90 : 10, flow rate 1 ml/min, *t*_R 8.29 min (–) and (–)-**14** (0.23 g, 15%) as colorless needles. *R*_f (heptane/AcOEt 4 : 1) 0.24. ¹H-NMR spectrum identical to **14**. M.p. 92.6–93.0°, [*α*]_D = –375.8 (*c* = 1 in CHCl₃), chiral HPLC (*Reprosil Chiral-NR*): heptane/EtOH 90 : 10, flow rate 1 ml/min, *t*_R 10.31 min (–).

Methyl (1*S*,4*S*,5*R*,6*R*)-4-[(tert-Butoxycarbonyl)amino]bicyclo[3.1.0]hex-2-ene-6-carboxylate ((+)-**13**) and Methyl (1*S*,4*S*,5*R*,6*S*)-4-[(tert-Butoxycarbonyl)amino]bicyclo[3.1.0]hex-2-ene-6-carboxylate ((+)-**14**). Using the same sequence as above but starting with (1*R*,5*S*)-7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one ([*α*]_D = +87.1 (*c* = 1 in CHCl₃) ([*α*]_D = +83.9 (*c* = 0.75 in CHCl₃) [20]) afforded (+)-**13** (1.46 g), *R*_f (heptane/AcOEt 4 : 1) 0.40. ¹H-NMR spectrum identical to **13**. M.p. 83.8–84.4°, [*α*]_D = +181.5 (*c* = 1 in CHCl₃), chiral HPLC (*Reprosil Chiral-NR*): heptane/EtOH 90 : 10, flow rate 1 ml/min, *t*_R 10.60 min (+) and (+)-**14** (0.49 g) as colorless needles, *R*_f (heptane/AcOEt 4 : 1) 0.24. ¹H-NMR spectrum identical to **14**. M.p. 91.9–92.4°, [*α*]_D = +368.5 (*c* = 1 in CHCl₃), chiral HPLC (*Reprosil Chiral-NR*): heptane/EtOH 90 : 10, flow rate 1 ml/min, *t*_R 9.79 min (+) were obtained.

(1*R*,2*R*,5*S*,6*S*)-3-(tert-Butoxycarbonyl)-6-(methoxycarbonyl)-4-oxo-3-azabicyclo[3.1.0]hexane-2-carboxylic Acid ((+)-**15**). To a stirred soln. of (+)-**13** (506 mg, 2 mmol) in a mixture of MeCN (6 ml), CCl₄ (6 ml), and H₂O was added NaIO₄ (1.75 g, 8.19 mmol) followed by RuCl₃ (9.91 mg, 0.044 mmol) at

ambient temp. After stirring for 4 h, the mixture was diluted with CH_2Cl_2 (15 ml) and H_2O (10 ml). The phases were separated, and the aq. phase was extracted with CH_2Cl_2 (2×20 ml). The combined org. extracts were dried (Na_2SO_4), filtered, and concentrated to give 0.565 g of light-red foam, which was purified by FC (AcOEt/AcOH 95:5 to give (+)-**15** (543 mg, 90%) as white solid. An anal. sample was recrystallized (AcOEt), ^1H -NMR spectrum identical to **15**. M.p. 117.2–118.5°. $[\alpha]_{\text{D}} = +85.6$ ($c = 1$ in CHCl_3).

(1*S*,2*S*)-3-[(*R*)-Amino(carboxy)methyl]cyclopropane-1,2-dicarboxylate ((+)-**17**). A soln. of (+)-**15** (150 mg, 0.50 mmol) in 10% HCl (5 ml) was heated at 100° for 3 h. The soln. was cooled to r.t. and concentrated to deliver 178 mg of crude product, which was submitted to ion exchange chromatography (Dowex 50WX4, elution with 12.5% $\text{NH}_3 \cdot \text{H}_2\text{O}$) to give (+)-**17** (98 mg, 82%) as white, hygroscopic foam (diammonium salt), ^1H - und ^{13}C -NMR spectra identical to **17**, $[\alpha]_{\text{D}} = +22.3$ ($c = 1$ in H_2O).

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