A New Synthesis of 2-Azabicyclo[2.1.1]hexanes

Cyrille Lescop, Laurence Mévellec, and François Huet*

Laboratoire de Synthèse Organique, UMR CNRS 6011, Faculté des Sciences, Université du Maine, Avenue Olivier Messiaen, F-72085 Le Mans Cedex 9, France

fhuet@univ-lemans.fr

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An efficient synthesis of the 2-azabicyclo[2.1.1]hexane ring system has been accomplished starting from *cis*-cyclobut-3-ene-1,2-dicarboxylic anhydride **7**, which was prepared using a photochemical method. The key step of this new strategy involved a stereoselective electrophilic addition of phenylselenyl bromide to the double bond of cyclobutene dicarbamate **16** derived from **7**. The subsequent ring closure of **17a** in the presence of sodium hydride afforded the 2-azabicyclohexane compound **18** with a satisfying overall yield. Reductive removal of the phenylselenyl group and subsequent deprotection led rapidly to the amino derivative **4a** functionalized on the carbon ring. Syntheses of the hydroxy and carboxylic derivatives **4b,c** were then achieved from the intermediary disulfonamide **23**. Displacement of the activated amino group by potassium acetate yielded hydroxy derivative **4b** after three additional steps. Finally, oxidation of the alcohol function of **4b** under Jones conditions followed by hydrogenolysis afforded the carboxylic derivative **4c**, which is the first reported β-isomer of 2,4-methanoproline **1**.

Introduction

2,4-methanoproline **1** is a natural non-protein amino acid that was isolated in 1980 from the seeds of *Ateleia herbert smithii* Pittier, a legume growing on the coast of Costa Rica (Figure 1).[1] It is well-known for its strong antifeedant activity and protects the seeds of this plant against at least 100 predators in this habitat. This compound drew our attention not only for its biological activity, which makes it of potential use in agrochemistry, but also for its unusual bicyclic structure. Indeed, this amino acid contains the 2-azabicyclo[2.1.1]hexane skeleton. Since its discovery, 2,4-methanoproline has been used in the field of peptidomimetics as a constrained equivalent of L-proline to study its conformational properties in peptides.[2] Replacement of L-proline in small peptides with this new bicyclic compound resulted in a selective stabilization of the *trans* tertiary peptide bond conformation, which suggests that 2,4-methanoproline may be a useful L-proline analogue for polypeptide molecular design. More recently, Piotrowski synthesized a novel class of rigid nicotine analogues from this 2-azabicyclohexane ring system with the aim to obtain less toxic biologically active molecules.[3]

Two main approaches have been described to prepare the 1-substituted 2-azabicyclo[2.1.1]hexane skeleton. The first[4] involves an intramolecular [2 + 2] photocycloaddition of *N*-vinyl-*N*-allylamines derived from amino acids, and the second[5] uses an intramolecular cyclization of a substituted cyclobutylamine.[6] Nevertheless, neither of these routes are readily amenable to synthesis of analogues. Up to now, little work has been devoted to the preparation of derivatives of 2,4-methanoproline. De Kimpe and co-worker have reported an interesting 10-step synthesis of the 2-azabicyclo[2.1.1]hexane system **2**, unsubstituted on the ring carbons, which is based upon the final ring closure of 1-(*N*-alkylamino)-3-(chloromethyl)cyclobutane.[7] Unfortunately the overall yield is quite low (1.0−4.0%). Recently, the first synthesis of 5-hydroxy-2-azabicyclo[2.1.1]hexane **3** has been described by Krow et al.[8] This approach involves an original rearrangement of a bromohydrin. Access to the bicylic skeleton **3** is short and requires only four steps; however, the yield of the key reaction is only 17% and the major compound is an unrearranged bromohydrin (53%).[8a]

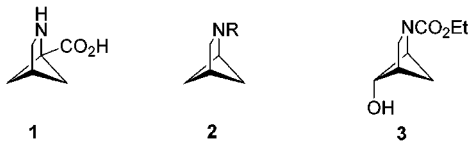

Figure 1.

* Tel: 33 2 43 83 33 38. Fax: 33 2 43 83 39 02.

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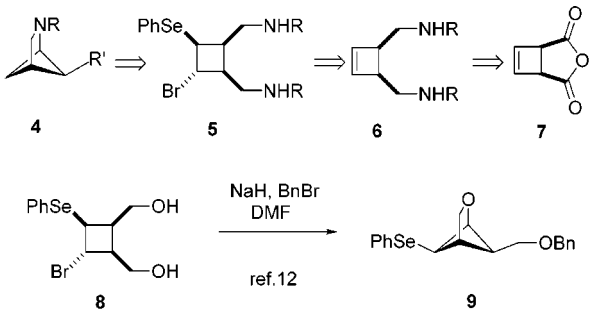
Scheme 1



In this paper, we report a new route to the synthesis of 5-substituted 2-azabicyclo[2.1.1]hexane **4** with different substituents R′ (Scheme 1). From our experience with cyclobutene chemistry, we envisaged using *cis*-cyclobut-3-ene-1,2-dicarboxylic anhydride **7** as the precursor.[9] It is one of the most useful cyclobutene starting materials because it can give rise to a wide range of compounds. For instance, anhydride **7** is the source of various carbocyclic nucleosides[10] and dienes.[11] Our approach consisted of the use of the suitable cyclobutene **6**, derived from **7**, bearing nitrogen substituents. A stereoselective electrophilic addition to the double bond of **6** followed by an intramolecular nucleophilic substitution involving cyclobutane **5** could afford the expected bicyclic structure. This new procedure would be an extension to the nitrogen series of our previous results on synthesis of the 2-oxabicyclo[2.1.1]hexane system **9** from the intramolecular cyclization of the dihydroxymethyl cyclobutane **8**.[12]

Results and Discussion

Synthesis of the Amino Derivative 4a. The starting anhydride **7** has been synthesized in two steps from the commercially available *trans*-dichloroethene **10** and maleic anhydride **11** using a photochemical method already described in a previous work (Scheme 2).[9a] As shown in Scheme 2, reduction of cyclobutene anhydride **7** with lithium aluminum hydride in THF at reflux provided diol **12** in excellent yield.[11c] The latter was converted to diamine **15** under standard conditions.[13] Treatment of diol **12** with methanesulfonyl chloride and triethylamine,[12] followed by nucleophilic substitution with sodium azide at 70 °C in DMF afforded diazide **14** in 75% isolated yield. The latter compound is quite unstable even at low temperatures (−18 °C) and must be used quickly for the next step after purification by column chromatography. Diamine **15** was then prepared by reduction of the azide functions with lithium aluminum hydride. As purification of this crude polar diamine was tricky, we used it as such in the next step. When it was subjected to reaction with di-*tert*-butyl dicarbonate in methanol,[14] the expected dicarbamate **16** was easily obtained.

We had noticed that haloselenylation reactions of cyclobutenes with oxygen substituents proceeded with excellent stereoselectivities,[12] and thus we have anticipated that cyclobutene dicarbamate **16** would lead to similar results. We were pleased to observe that, in this case, reaction also worked with a good selectivity in favor of the electrophilic attack *syn* to the nitrogen substituents. The expected compound **17** was obtained in 86% isolated yield as a mixture of two diastereomers, **17a**:**17b** = 85:15. The isomers could be separated by column chromatography. On the other hand, attempts to haloselenylate the non protected diamine **15** failed. No selectivity was observed, and the reaction did not go quickly to completion (35% conversion in 24 h). The high preference of **16** for *syn*-attack is likely to be due to stabilization of the intermediary selenonium ion by the lone pair of nitrogen atoms.[15] Configurations of **17a** and **17b** were assigned by several NMR experiments (Figure 2). Carbon atoms linked to the phenylselenyl group were assessed on the basis of coupling with ^{77}Se: $J_{C-1/Se} = 89.1$ Hz for **17a** and $J_{C-1/Se} = 91.0$ Hz for **17b**. The subsequent ^{1}H/^{13}C HETCOR correlations led to assignments of the corresponding cyclobutane proton H-1, then to the other ones by successive ^{1}H/^{1}H spin decoupling experiments. At last, the stereochemistry of compounds **17a** and **17b** were unequivocally established on the basis of ^{1}H/^{1}H correlations observed in the phase-sensitive NOESY spectra. The major isomer **17a** corresponds to the *cis*-*cis* relative relationships between protons H-1, H-3, and H-4. The bromine atom, in an *anti* relationship to the carbamate groups, is then in the suitable position to generate the bicyclic system by an intramolecular substitution.

Further treatment of compound **17a** with sodium hydride in DMF led to the expected ring closure, thus providing the 2-azabicyclo[2.1.1]hexane structure **18** (Scheme 3). This reaction has to be carried out in a dilute medium (0.02 M) to minimize the intermolecular nucleophilic substitution, and a reasonable yield (71%) was obtained. When we increased the scale slightly (0.07 M concentration) the yield diminished (54%). Both ^{1}H and ^{13}C NMR spectra are quite complex because, at room temperature, two conformations are in equilibrium due to the slow inversion of the nitrogen atom of the bicyclic skeleton or to the carbamate resonance. The structure of **18** was assigned by ^{1}H NMR. Indeed, protons H-1 at δ 4.41 and 4.32 and H-4 at δ 2.84 and 2.80 show a four bond coupling, $J_{1/4} = 6.7$ Hz. This value is in agreement with a 2-azabicyclo[2.1.1]hexane system since it is typical for the coupling of bridgehead protons. Similar coupling constants (6.3−6.9 Hz) were measured for compounds **2**[7] and **3**.[8a] Subsequent reductive removal of the phenylselenyl group from bicyclic compound **18** with tributyltin hydride in the presence of AIBN afforded the protected amino derivative **19** in excellent yield.[16] Deprotection of

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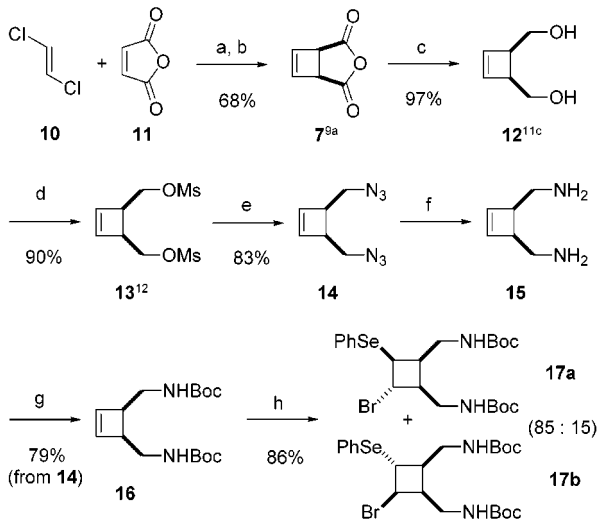
Scheme 2[a]



[a] Reagents and conditions: (a) *hν*, EtOAc; (b) Zn, Ac_2O, toluene, 80 °C; (c) $LiAlH_4$, THF, reflux; (d) MsCl, Et_3N, CH_2Cl_2; (e) NaN_3, DMF, 75 °C; (f) $LiAlH_4$, THF, reflux; (g) Boc_2O, Et_3N, DMAP, MeOH; (h) PhSeBr, CH_2Cl_2.

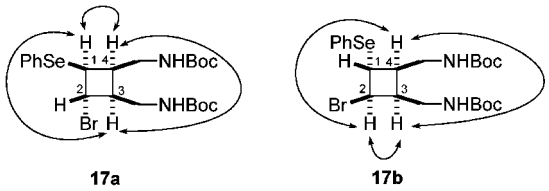
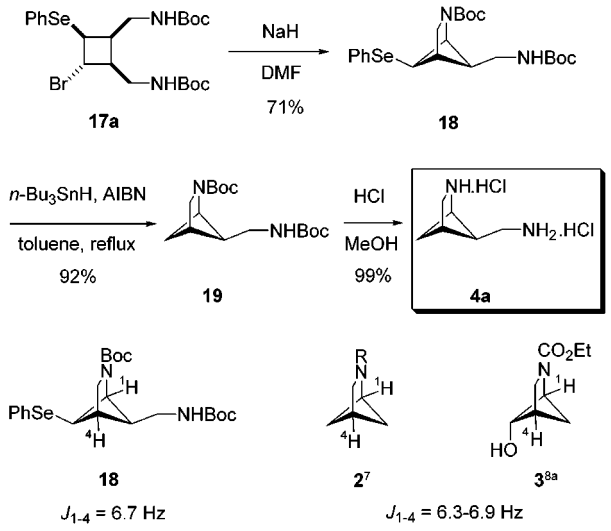


Figure 2. Significant phase-sensitive NOESY correlations.

Scheme 3



the carbamate groups was achieved by treatment with gaseous hydrogen chloride in methanol to provide quantitatively dihydrochloride of 5-methylamino-2-azabicyclo-[2.1.1]hexane **4a**. Thus, this new strategy, which gives a better yield (30%) than the previous ones, allowed us to prepare easily the 2-azabicyclo[2.1.1]hexane **18** in a multigram scale. Furthermore, this key intermediate **18** led to the amino derivative **4a**, functionalized on the carbon ring, which was then obtained in nine steps from cyclobutene anhydride **7** with a satisfying 27% overall yield.

Synthesis of the Hydroxy and Carboxylic Derivatives 4b,c. This good result encouraged us to synthesize bicyclic compounds **4b,c** substituted by a hydroxylmethyl or carboxylic acid group, as those molecules could exhibit interesting biological properties (Scheme 4). To achieve the conversion of the amine function of compound **19** or **4a** into a hydroxymethyl group, we used an intermediary disulfonamide leaving group. We encountered difficulties when trying to regenerate the amine functions of **19** upon treatment with trifluoroacetic acid in dichloromethane. This problem was overcome by the use of the seleno compound **18**, which led under the same experimental conditions to a less polar diamine **20**. This crude diamine was thus obtained quantitatively, and the subsequent synthesis of the disulfonamide **23** was then achieved in two steps using tosyl chloride. For the first stage, the reaction was performed in dichloromethane instead of DMF. Although the latter is known to be the suitable solvent for this kind of reaction,[17] in our case DMF induced a partial formylation of sulfonamide **21** into **22**. Moreover, the reaction with the secondary amine function could not be avoided because it already takes place in the first step even when using 1 equiv of tosyl chloride. This is the reason we used an excess of reagent to transform **20** into sulfonamide **21** alone. The latter was isolated in 66% yield after column chromatography. Further treatment of **21** with sodium hydride and tosyl chloride in DMF afforded the disulfonamide **23** in excellent yield and without formylation. Displacement of the activated amino group was then achieved with potassium acetate in the presence of potassium iodide in HMPA according to the method of Andersen et al.[17] The expected acetate **24** was obtained in high yield together with a small amount of compound **21** (13%) resulting from a N−S bond cleavage. Such a side reaction is well-known in this kind of substitution.[18] However, sulfonamide **21** could be recycled. Tributyltin hydride mediated removal of the phenylselenyl group from **24** then afforded the desired compound **25** in 77% yield.

Subsequently, we envisioned that the tosyl group could be removed from the nitrogen atom in a final step to generate the *β*-amino acid **4c**. The *N*-toluenesulfonyl group has been reported to be cleaved with 32% hydrobromic acid in acetic acid.[19] Unfortunately, this standard

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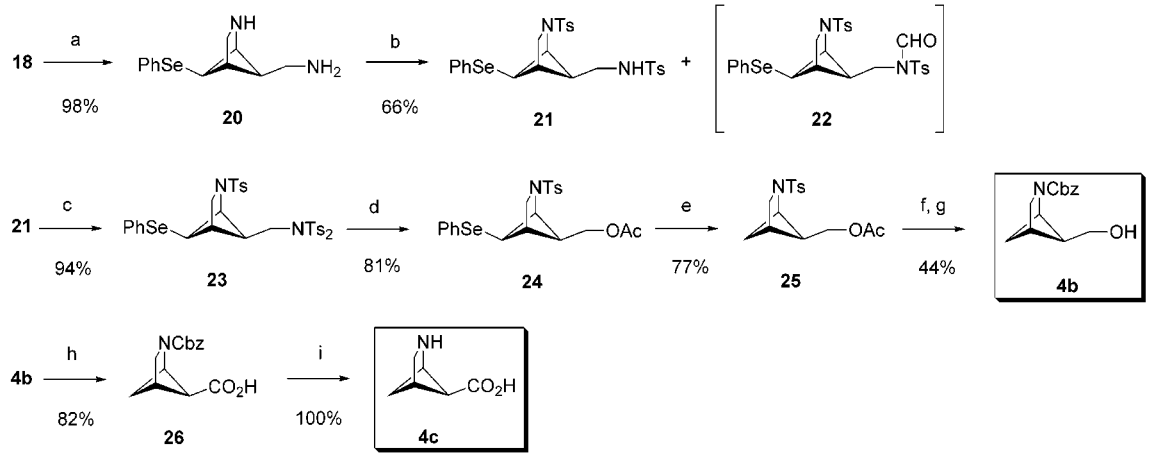
Scheme 4[a]



[a] Reagents and conditions: (a) CF_3CO_2H/CH_2Cl_2 1:1; (b) TsCl, Et_3N, CH_2Cl_2; (c) TsCl, NaH, DMF; (d) KOAc, KI, HMPA, 120 °C; (e) *n*-Bu_3SnH, AIBN, toluene, reflux; (f) 32% HBr/AcOH, EtOAc; (g) CbzCl, 1 M NaOH, dioxane; (h) CrO_3, H_2SO_4, acetone, −5 °C; (i) H_2, Pd/C, MeOH.

method failed to provide the expected amino acid hydrobromide. Alternative deprotection procedures involving 48% aqueous hydrobromic acid,[20] sodium in liquid ammonia,[18] or sodium naphthalenide[21] in THF were also unfruitful and gave only decomposition products, and no reaction occurred with magnesium in methanol.[22] We then examined the deprotection in an earlier step. Exposure of acetate **25** to 32% HBr in acetic acid in a sealed tube resulted in the formation of the corresponding amino alcohol hydrobromide after detosylation and simultaneous hydrolysis of the ester function. The latter was purified via its benzyloxycarbonyl derivative **4b**, which was prepared in moderate yield by treatment with benzyl chloroformate. Further oxidation of the hydroxy compound **4b** under Jones conditions gave the corresponding carboxylic acid **26** in 82% yield. Finally, hydrogenolysis of **26** afforded quantitatively the free β-amino acid **4c** which is an isomer of 2,4-methanoproline **1**.

In conclusion, we have described a new efficient strategy for the synthesis of the 2-azabicyclo[2.1.1]hexane system using the ring closure of a cyclobutane intermediate. This method is convenient for the multigram-scale preparation of a compound with skeleton **18** and has the potential to provide several functionalized derivatives. Biological evaluations of the new 5-substituted 2-azabicyclo[2.1.1]hexanes **4a**−**c** in crop protection have shown no significant activity. To the best of our knowledge, it is the first time that a β-isomer of 2,4-methanoproline has been prepared. In the field of peptidomimetics, it may be interesting to incorporate the latter into peptides as a proline constrained analogue and to study the resulting conformational effects.

Experimental Section

General. All moisture-sensitive reactions were carried out in oven-dried glassware (110 °C) under nitrogen atmosphere. Commercially available reagents and solvents were purified and dried, when necessary, by standard methods just prior to use. IR spectra were scanned on a FT infrared spectrophotometer. All melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100.6 MHz, respectively. Chemical shifts are reported in ppm downfield from TMS, which was used as the internal reference. In D_2O solution, TMS was replaced by DSS. Multiplicities in the ^{13}C spectra were determined by DEPT experiments, and numerous assignments were obtained by ^{13}C/^{1}H HETCOR and HMBC experiments. Ratios in mixtures of diastereomers were calculated from ^{1}H NMR. Elemental analyses were obtained from the Service de Microanalyse, CNRS ICSN, Gif-sur-Yvette. High-resolution mass measurements were performed at the CRMPO, Rennes.

***cis*-3,4-Bis(azidomethyl)cyclobut-1-ene (14).** To a solution of dimesylate **13**[12] (18.64 g, 68.95 mmol) in anhydrous DMF (190 mL) was added sodium azide (9.43 g, 145.05 mmol) portionwise. The reaction mixture was then stirred at 75 °C for 3 h. After cooling to room temperature, the mixture was poured into ice-cold water (350 mL). The aqueous layer was then extracted with Et_2O (5 × 220 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by column chromatography (silica gel, cyclohexane/EtOAc; 1/0 → 94/6) afforded diazide **14** (9.45 g, 83%) as a colorless oil: IR (neat) 2094, 1263 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.20 (s, 2H, H-1 and H-2), 3.49−3.44 (m, 4H, H-5 and H-6), 3.23 (m, 2H, H-3 and H-4); ^{13}C NMR ($CDCl_3$) δ 138.5 (C-1 and C-2), 51.3 (C-5 and C-6), 45.04 (C-3 and C-4); HRMS calcd for $[(C_6H_8N_6) - 2N_2]^+$ 108.0687, found 108.0691.

***cis*-3,4-Bis(aminomethyl)cyclobut-1-ene (15).** A solution of diazide **14** (8.85 g, 53.90 mmol) in anhydrous THF (60 mL) was added to a suspension of $LiAlH_4$ (6.46 g, 161.71 mmol) in anhydrous THF (90 mL) at 0 °C under N_2 atmosphere. When the addition was complete, the mixture was heated at reflux for 18 h. After cooling to 0 °C, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and then hydrolyzed with water (12.5 mL). The granular white solid was filtered off and washed several times with CH_2Cl_2 (100 mL). The latter was then extracted for 12 h in a Soxhlet thimble with THF. Both organic layers were combined and concentrated under reduced pressure to afford the crude diamine **15** (6.78 g) as a pale yellow oil which was used as such for the next step: IR (neat) 3317, 3045, 1590, 1481 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.08 (s, 2H, H-1 and H-2), 5.68 (br s, 4H, NH_2), 3.34 (m, 2H, H-3 and H-4, J = 10.1, 3.5 Hz), 3.24 (dd, 2H, H-5 and H-6, J = 12.8, 3.5 Hz), 2.82 (dd, 2H, H-5′ and H-6′, J = 12.8, 10.1 Hz); ^{13}C NMR ($CDCl_3$) δ 137.8 (C-1 and C-2), 45.4 (C-3 and C-4), 39.9 (C-5 and C-6); HRMS calcd for $C_6H_{12}N_2$ 112.1000, found 112.1001.

***cis*-3,4-Bis(*tert*-butoxycarbonylaminomethyl)cyclobut-1-ene (16).** Triethylamine (16.70 mL, 0.12 mol) and DMAP (14.70 g, 0.12 mol) were added to a solution of crude diamine

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15 (6.78 g) in anhydrous MeOH (120 mL). The mixture was cooled to 0 °C, and Boc_2O (52.80 g, 0.24 mol) was added portionwise. The reaction mixture was then stirred at room temperature for 2 h. After evaporation of the solvent the yellow residue was dissolved in CH_2Cl_2 (500 mL) and washed successively with 0.3 M $KHSO_4$ (350 mL), H_2O (100 mL), and brine (100 mL). Drying of the organic layer over $MgSO_4$ and evaporation of the solvent gave the crude compound, which was chromatographed (silica gel, cyclohexane/EtOAc; 9/1 → 4/1) to lead to dicarbamate **16** (13.24 g, 79% from diazide **14**) as white crystals: mp 131−132 °C (petroleum ether/CH_2Cl_2); IR (KBr) 3370, 1687, 1525, 1172 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.12 (s, 2H, H-1 and H-2), 4.80 (br s, 2H, NH), 3.28 (m, 4H, H-5 and H-6), 3.06 (m, 2H, H-3 and H-4), 1.44 (s, 18H, $(CH_3)_3C$); ^{13}C NMR ($CDCl_3$) δ 156.0 (*C*═O), 138.5 (C-1 and C-2), 79.3 ($(CH_3)_3C$), 46.0 (C-3 and C-4), 40.4 (C-5 and C-6), 28.4 ($(CH_3)_3C$). Anal. Calcd for $C_{16}H_{28}N_2O_4$: C, 61.51; H, 9.03; N, 8.97. Found: C, 61.56; H, 8.88; N, 8.72.

(1*S,2*S**,3*S**,4*R**)-2-Bromo-3,4-bis(*N*-*tert*-butoxycarbonylaminomethyl)-1-phenylselenylcyclobutane (17a) and (1*S**,2*S**,3*R**,4*S**)-2-Bromo-3,4-bis(*N*-*tert*-butoxycarbonylaminomethyl)-1-phenylselenylcyclobutane (17b).** A solution of phenylselenyl bromide (10.31 g, 42.82 mmol) in anhydrous CH_2Cl_2 (190 mL) was added dropwise to a solution of cyclobutene dicarbamate **16** (13.11 g, 41.96 mmol) in anhydrous CH_2Cl_2 (130 mL) at 0 °C under N_2 atmosphere. The reaction mixture was then stirred at room temperature overnight, and the solvent was evaporated in vacuo. The ratio of isomers, **17a**:**17b** = 85:15, was measured by ^1H NMR of the residue. Purification by column chromatography (silica gel, cyclohexane/EtOAc; 1/0 → 5/1) afforded seleno compounds **17a** (16.78 g, 73%) and **17b** (3.02 g, 13%) both as white crystals. Major isomer **17a**: mp 165−166 °C (petroleum ether/CH_2Cl_2); IR (KBr) 3361, 1681, 1519, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.54 (m, 2H, H arom), 7.28 (m, 3H, H arom), 5.21 (br s, 1H, NH), 4.73 (br s, 1H, NH), 4.11 (m, 1H, H-2), 4.06 (m, 1H, H-1), 3.39 (m, 2H, H-5), 3.32 (m, 1H, H-6), 3.25 (m, 1H, H-6′), 2.99 (m, 1H, H-4), 2.86 (m, 1H, H-3), 1.44 (s, 9H, $(CH_3)_3C$), 1.42 (s, 9H, $(CH_3)_3C$); ^{13}C NMR ($CDCl_3$) δ 155.9 (*C*═O), 155.7 (*C*═O), 133.4 (*C*H, arom), 129.3 (*C*H, arom), 129.0 (quat C, arom), 127.7 (*C*H, arom), 79.7 ($(CH_3)_3C$), 79.5 ($(CH_3)_3C$), 48.5 (C-1), 47.4 (C-2), 47.3 (C-3), 41.2 (C-4), 39.3 (C-6), 38.9 (C-5), 28.4 ($(CH_3)_3C$), 28.3 ($(CH_3)_3C$), J ($^{13}C/^{77}Se$) = 89 Hz. Anal. Calcd for $C_{22}H_{33}N_2O_4BrSe$: C, 48.19; H, 6.06; N, 5.11; Br, 14.57; Se, 14.40. Found: C, 48.03; H, 6.06; N, 5.16; Br, 14.53; Se, 14.37. Minor isomer **17b**: mp 154−155 °C (petroleum ether/CH_2Cl_2); IR (KBr) 3365, 1681, 1519, 1168 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.61 (m, 2H, H arom), 7.33 (m, 3H, H arom), 5.16 (br s, 1H, NH), 4.83 (br s, 1H, NH), 4.20 (m, 1H, H-2), 3.65 (m, 1H, H-1), 3.43 (m, 2H, H-6), 3.32 (m, 2H, H-5), 2.72 (m, 1H, H-3), 2.33 (m, 1H, H-4), 1.45 (s, 9H, $(CH_3)_3C$), 1.41 (s, 9H, $(CH_3)_3C$); ^{13}C NMR ($CDCl_3$) δ 155.8 (*C*═O), 155.6 (*C*═O), 136.4 (*C*H, arom), 129.2 (*C*H, arom), 128.6 (*C*H, arom), 126.3 (quat C, arom), 79.5 ($(CH_3)_3C$), 48.2 (C-2), 47.9 (C-1), 41.6 (C-3), 41.3 (C-4), 39.8 (CH_2), 39.0 (CH_2), 28.4 ($(CH_3)_3C$), 28.3 ($(CH_3)_3C$), J ($^{13}C/^{77}Se$) = 91 Hz. Anal. Calcd for $C_{22}H_{33}N_2O_4BrSe$: C, 48.19; H, 6.06; N, 5.11; Br, 14.57; Se, 14.40. Found: C, 47.98; H, 6.04; N, 4.92; Br, 14.71; Se, 14.22.

(1*S,4*S**,5*R**,6*R**)-2-*N*-*tert*-Butoxycarbonyl-6-*N*-*tert*-butoxycarbonylaminomethyl-5-phenylselenyl-2-azabicyclo[2.1.1]hexane (18).** Sodium hydride (60% dispersion in mineral oil, 1.40 g, 35.00 mmol) was added portionwise to a solution of compound **17a** (6.39 g, 11.65 mmol) in anhydrous DMF (610 mL) at 0 °C. The mixture was then stirred at room temperature for 2 days. Water (0.4 mL) was added, and solvent was removed under reduced pressure. Purification of the residue by column chromatography (silica gel, cyclohexane/EtOAc; 5/1 → 5/2) provided bicyclic compound **18** (3.87 g, 71%) as a white solid: mp 135−137 °C; IR (KBr) 3365, 2975, 1687, 1388, 1172 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51 (m, 1H, H arom), 7.47 (m, 1H, H arom), 7.25 (m, 3H, H arom), 4.63 (br s, 0.5H, NH), 4.56 (br s, 0.5H, NH), 4.41 (m, 0.5H, H-1, J = 6.7 Hz), 4.32 (m, 0.5H, H-1, J = 6.7 Hz), 3.51 (d, 0.5H, H-3, J = 9.7 Hz), 3.44 (m, 1.5H, H-5 and H-3), 3.25 (d, 1H, H-3′, J = 9.7 Hz), 3.19 (m, 0.5H, H-7), 3.06 (m, 0.5H, H-7), 2.90 (m, 0.5H, H-7′), 2.84 (m, 0.5H, H-4), 2.80 (m, 0.5H, H-4), 2.71 (m, 0.5H, H-7′), 2.22 (m, 0.5H, H-6), 2.15 (m, 0.5H, H-6), 1.51 (s, 4.5H, $(CH_3)_3C$), 1.46 (s, 4.5H, $(CH_3)_3C$), 1.43 (s, 4.5H, $(CH_3)_3C$), 1.42 (s, 4.5H, $(CH_3)_3C$); ^{13}C NMR ($CDCl_3$) δ 157.1 (*C*═O), 156.9 (*C*═O), 155.9 (*C*═O), 155.8 (*C*═O), 133.8 (*C*H, arom), 133.0 (*C*H, arom), 129.4 (quat C, arom), 129.1 (*C*H, arom), 129.0 (*C*H, arom), 127.3 (*C*H, arom), 127.1 (*C*H, arom), 80.1 ($(CH_3)_3C$), 79.7 ($(CH_3)_3C$), 79.5 ($(CH_3)_3C$), 79.4 ($(CH_3)_3C$), 64.6 (*C*H), 63.7 (*C*H), 47.9 (*C*H), 47.8 (*C*H), 45.9 (*C*H); 45.4 (*C*H), 44.7 (CH_2), 44.1 (*C*H), 44.0 (CH_2), 43.9 (*C*H), 36.9 (CH_2), 28.4 ($(CH_3)_3C$), 28.3 ($(CH_3)_3C$). Anal. Calcd for $C_{22}H_{32}N_2O_4Se$: C, 56.53; H, 6.90; N, 5.99; Se, 16.89. Found: C, 56.23; H, 6.64; N, 6.04; Se, 16.60.

(1*R,4*S**,5*R**)-2-*N*-*tert*-Butoxycarbonyl-5-*N*-*tert*-butoxycarbonylaminomethyl-2-azabicyclo[2.1.1]hexane (19).** To a solution of seleno compound **18** (1.60 g, 3.42 mmol) in freshly distilled toluene (18.5 mL) were added *n*-Bu_3SnH (2.76 mL, 10.26 mmol) and a solution of AIBN (0.02M) in toluene (5.13 mL, 0.10 mmol). The mixture was degassed with a steam of N_2 for 15 min, and heated to reflux for 12 h. The reaction mixture was then cooled to room temperature, and the solvent was removed in vacuo. The residue was purified by column chromatography (silica gel, cyclohexane/EtOAc: 98/2 → 7/3) followed by a recrystallization (iPr_2O) to afford compound **19** (984 mg, 92%) as white crystals: mp 86−87 °C; IR (KBr) 3384, 1720, 1687, 1520, 1182 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.60 (br s, 0.5H, NH), 4.49 (br s, 0.5H, NH), 4.30 (d, 0.5H, H-1, J = 5.6 Hz), 4.21 (d, 0.5H, H-1, J = 5.6 Hz), 3.22 (m, 2H, H-3), 3.09 (m, 0.5H, H-7), 2.95 (m, 0.5H, H-7), 2.70 (m, 1.5H, H-7′ and H-4), 2.53 (m, 0.5H, H-7′), 2.17 (m, 1H, H-5); 1.69 (m, 1H, H-6), 1.47 (s, 9H, $(CH_3)_3C$), 1.43 (s, 9H, $(CH_3)_3C$), 1.32 (m, 1H, H-6′); ^{13}C NMR ($CDCl_3$) δ 156.7 (*C*═O), 156.5 (*C*═O), 156.0 (*C*═O), 155.8 (*C*═O), 79.5 ($(CH_3)_3C$), 79.4 ($(CH_3)_3C$), 79.2 ($(CH_3)_3C$), 61.3 (*C*H), 60.2 (*C*H), 47.7 (*C*H), 47.6 (*C*H), 46.3 (CH_2), 45.5 (CH_2), 39.4 (*C*H), 39.1 (*C*H), 37.8 (CH_2), 37.6 (CH_2), 36.6 (CH_2), 28.4 ($(CH_3)_3C$), 28.3 ($(CH_3)_3C$). Anal. Calcd for $C_{16}H_{28}N_2O_4$: C, 61.51; H, 9.03; N, 8.97. Found: C, 61.63; H, 9.02; N, 8.91.

(1*R,4*S**,5*R**)-5-Aminomethyl-2-azabicyclo[2.1.1]hexane Dihydrochloride (4a).** A saturated solution of HCl in MeOH (16.0 mL) was added with stirring to a solution of bicyclo dicarbamate **19** (250 mg, 0.80 mmol) in MeOH (1.0 mL) at −5 °C. The mixture was stirred at room temperature for 3 h, and then N_2 was bubbled for 2 h to remove the excess of gaseous HCl. The solvent was evaporated under reduced pressure, and the yellow residue was stirred at reflux in a solution of Et_2O/MeOH (1/1) to provide, after filtration, the amino dihydrochloride **4a** (146 mg, 99%) as a white solid: dec 246 °C; IR (KBr) 3300−2400, 1610, 1525 cm^{-1}; ^1H NMR (D_2O) δ 4.28 (m, 1H, H-1, J = 6.1, 1.0 Hz), 3.41 (d, 1H, H-3, J = 11.0 Hz), 3.39 (d, 1H, H-3′, J = 11.0 Hz), 3.04 (m, 1H, H-4, J = 6.1 Hz), 2.93 (dd, 1H, H-7, J = 13.9, 7.1 Hz), 2.88 (dd, 1H, H-7′, J = 13.9, 7.8 Hz), 2.57 (m, 1H, H-5, J = 7.8, 7.1 Hz), 2.02 (m, 1H, H-6, J = 9.5, 1.0 Hz), 1.43 (d, 1H, H-6′, J = 9.5 Hz); ^{13}C NMR (D_2O) δ 62.0 (*C*H), 45.3 (CH_2), 44.2 (*C*H), 40.6 (*C*H), 36.3 (CH_2), 35.7 (CH_2). Anal. Calcd for $C_6H_{14}N_2Cl_2$: C, 38.93; H, 7.62; N, 15.13; Cl, 38.31. Found: C, 38.73; H, 7.47; N, 15.12; Cl, 38.16; HRMS calcd for $[(C_6H_{14}N_2Cl_2) - H - 2(HCl)]^+$ 111.0922, found 111.0922.

(1*S,4*S**,5*R**,6*R**)-6-Aminomethyl-5-phenylselenyl-2-azabicyclo[2.1.1]hexane (20).** Trifluoroacetic acid (14.5 mL) was added to a solution of compound **18** (2.37 g, 5.07 mmol) in CH_2Cl_2 (14.5 mL) at 0 °C. The mixture was stirred at room temperature for 2 h and then cooled to 0 °C. A 20% NaOH solution was carefully added until pH 10, and the mixture was extracted with CH_2Cl_2 (10 × 80 mL). The combined organic layers were washed with brine (60 mL), dried over K_2CO_3, and concentrated under reduced pressure to yield crude diamine **20** (1.33 g, 98%) as a pale yellow oil: IR (neat) 3500−3200, 2985, 1577, 1477, 735, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46 (m, 2H, arom), 7.24 (m, 3H, arom), 3.59 (m, 1H, H-1, J = 6.0 Hz), 3.36 (m, 1H, H-5), 2.89 (d, 1H, H-3, J = 9.7 Hz), 2.81 (m, 1H, H-4, J = 6.0 Hz), 2.75 (d, 1H, H-3′, J = 9.7 Hz), 2.68 (dd, 1H, H-7, J = 12.8, 7.8 Hz), 2.58 (dd, 1H, H-7′, J = 12.8, 6.2 Hz), 1.80 (m, 1H, H-6, J = 7.8, 6.2 Hz), 1.63 (br s, 3H, NH and NH_2); ^{13}C NMR ($CDCl_3$) δ 132.8 (*C*H, arom), 129.6 (quat C, arom), 129.0 (*C*H, arom), 126.9 (*C*H, arom), 61.6 (*C*H), 48.6

(*C*H), 46.9 (*C*H), 44.6 (*C*H), 42.1 (*C*H_2), 38.0 (*C*H_2); HRMS calcd for $C_{12}H_{16}N_2Se$ 268.0479, found 268.0491.

(1*S,4*S**,5*R**,6*R**)-5-Phenylselenyl-2-*N*-*p*-toluenesulfonyl-6-*N*-(*p*-toluenesulfonyl)-aminomethyl-2-azabicyclo-[2.1.1]hexane (21).** To a solution of diamine **20** (0.64 g, 2.39 mmol) in anhydrous CH_2Cl_2 (6.6 mL) at 0 °C were added triethylamine (1.33 mL, 9.57 mmol) and tosyl chloride (1.60 g, 8.39 mmol) portionwise under N_2 atmosphere. The mixture was then stirred at room temperature for 16 h. After cooling to 0 °C, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with 10% HCl (100 mL). The aqueous layer was extracted twice with CH_2Cl_2 (2 × 100 mL). The combined organic layers were then dried over $MgSO_4$ and concentrated in vacuo. The orange residue was purified by column chromatography (silica gel, cyclohexane/EtOAc; 9/1 → 7/3) to afford compound **21** (0.91 g, 66%) as white crystals: mp 150−151 °C (Et_2O/CH_2Cl_2); IR (KBr): 3269, 1340, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.79 (m, 2H, arom), 7.73 (m, 2H, arom), 7.31 (m, 6H, arom), 7.27−7.18 (m, 3H, arom), 5.04 (dd, 1H, NH, J = 8.8, 4.7 Hz), 4.22 (ddd, 1H, H-1, J = 6.6, 1.6, 1.2 Hz), 3.51 (d, 1H, H-3, J = 8.6 Hz), 3.47 (d, 1H, H-3′, J = 8.6 Hz), 3.44 (dd, 1H, H-5, J = 2.7, 1.6 Hz), 3.00 (ddd, 1H, H-7, J = 14.1, 8.8, 6.2 Hz), 2.88 (ddd, 1H, H-4, J = 6.6, 2.8, 2.7 Hz), 2.78 (ddd, 1H, H-7′, J = 14.1, 9.1, 4.7 Hz), 2.43 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.34 (m, 1H, H-6, J = 9.1, 6.2, 2.8, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 143.5 (quat C, arom), 143.4 (quat C, arom), 138.2 (quat C, arom), 136.9 (quat C, arom), 133.2 (*C*H, arom), 129.7 (*C*H, arom), 129.6 (*C*H, arom), 129.2 (*C*H, arom), 128.9 (quat C, arom), 127.4 (*C*H, arom), 127.0 (*C*H, arom), 126.8 (*C*H, arom), 66.9 (*C*H), 48.2 (*C*H), 45.8 (*C*H), 45.6 (*C*H_2), 44.2 (*C*H), 39.5 (*C*H_2), 21.6 (*C*H_3), 21.5 (*C*H_3). Anal. Calcd for $C_{26}H_{28}N_2O_4S_2$-Se: C, 54.25; H, 4.90; N, 4.87; S, 11.14. Found: C, 54.03; H, 4.83; N, 4.74; S, 11.18.

(1*S,4*S**,5*R**,6*R**)-5-Phenylselenyl-2-*N*-*p*-toluenesulfonyl-6-*N*-(*p*-toluenesulfonyl)-formamidomethyl-2-azabicyclo[2.1.1]hexane (22).** If DMF was used as solvent for the preparation of **21**, the byproduct **22**, resulting from formylation reaction of **21**, was isolated. The quantity of **22** increased proportionally to the reaction time; after 48 h of stirring a mixture **21**/**22** in a 1.9:1 ratio was then obtained (overall yield = 58%): mp 148−150 °C (Et_2O/CH_2Cl_2); IR (KBr) 3448, 1693, 1358, 1346, 1192, 1163 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.04 (s, 1H, CHO), 7.81 (m, 2H, arom), 7.73 (m, 2H, arom), 7.36 (m, 4H, arom), 7.31−7.19 (m, 5H, arom), 4.39 (ddd, 1H, H-1, J = 6.8, 1.5, 1.4 Hz), 3.76 (d, 1H, H-3, J = 8.5 Hz), 3.48 (d, 1H, H-3′, J = 8.5 Hz), 3.46 (dd, 1H, H-7, J = 14.9, 8.8 Hz), 3.41 (dd, 1H, H-5, J = 2.6, 1.5 Hz), 3.30 (dd, 1H, H-7′, J = 14.9, 3.5 Hz), 2.92 (ddd, 1H, H-4, J = 6.8, 2.7, 2.6 Hz), 2.47 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.31 (m, 1H, H-6, J = 8.8, 3.5, 2.7, 1.4 Hz); ^{13}C NMR ($CDCl_3$) δ 161.4 (*C*═O), 145.8 (quat C, arom), 143.2 (quat C, arom), 138.1 (quat C, arom), 134.1 (quat C, arom), 133.3 (*C*H, arom), 130.4 (*C*H, arom), 129.5 (*C*H, arom), 129.1 (*C*H, arom), 129.0 (quat C, arom), 127.5 (*C*H, arom), 127.4 (*C*H, arom), 127.0 (*C*H, arom), 67.8 (*C*H), 48.0 (*C*H), 45.7 (*C*H), 45.2 (*C*H_2), 45.1 (*C*H), 39.5 (*C*H_2), 21.7 (*C*H_3), 21.5 (*C*H_3). Anal. Calcd for $C_{27}H_{28}N_2O_5S_2Se{\cdot}0.2H_2O$: C, 53.41; H, 4.71; N, 4.61; S, 10.56; Se, 13.00. Found: C, 53.21; H, 4.66; N, 4.51; S, 10.72; Se, 12.86.

(1*S,4*S**,5*R**,6*R**)-5-Phenylselenyl-2-*N*-*p*-toluenesulfonyl-6-*N*,*N*-di-(*p*-toluenesulfonyl)-aminomethyl-2-azabicyclo[2.1.1]hexane (23).** Sodium hydride (60% dispersion in mineral oil, 201 mg, 5.02 mmol) was added portionwise to a solution of compound **21** (0.95 g, 1.65 mmol) in anhydrous DMF (53 mL) at 0 °C. The mixture was then stirred at room temperature for 15 min under N_2 atmosphere and cooled again to 0 °C. Tosyl chloride (635 mg, 3.33 mmol) was added portionwise, and the reaction mixture was stirred at room temperture overnight. Water (15 mL) was then added, and the aqueous solution was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the orange residue by column chromatography (silica gel, cyclohexane/EtOAc; 95/5 → 3/1) afforded ditosylamine **23** (1.13 g, 94%) as white crystals: 171−172 °C (Et_2O/CH_2Cl_2); IR (KBr) 1373, 1167, 1153, 815 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.82 (m, 2H, arom), 7.74 (m, 4H, arom), 7.36 (m, 2H, arom), 7.30 (m, 6H, arom), 7.25 (m, 3H, arom), 4.37 (m, 1H, H-1, J = 6.8 Hz), 3.66 (d, 1H, H-3, J = 8.6 Hz), 3.60 (d, 2H, H-7, J = 5.6 Hz), 3.47 (d, 1H, H-3′, J = 8.6 Hz), 3.39 (m, 1H, H-5), 2.90 (m, 1H, H-4, J = 6.8 Hz), 2.45 (s, 6H, 2 × CH_3), 2.42 (s, 3H, CH_3), 2.41 (m, 1H, H-6, J = 5.6 Hz); ^{13}C NMR ($CDCl_3$) δ 145.1 (quat C, arom), 143.2 (quat C, arom), 138.1 (quat C, arom), 136.1 (quat C, arom), 133.3 (*C*H, arom), 129.7 (*C*H, arom), 129.5 (*C*H, arom), 129.2 (*C*H, arom), 129.1 (quat C, arom), 128.2 (*C*H, arom), 127.4 (*C*H, arom), 127.0 (*C*H, arom), 67.9 (*C*H), 47.9 (*C*H), 46.4 (*C*H), 45.8 (*C*H), 45.6 (*C*H_2), 45.1 (*C*H_2), 21.6 (*C*H_3), 21.5 (*C*H_3). Anal. Calcd for $C_{33}H_{34}N_2O_6S_3Se$: C, 54.31; H, 4.70; N, 3.84; S, 13.18; Se, 10.83. Found: C, 54.21; H, 4.61; N, 3.88; S, 13.18; Se, 10.50.

(1*S,4*S**,5*R**,6*S**)-6-Acetoxymethyl-5-phenylselenyl-2-*N*-*p*-toluenesulfonyl-2-aza-bicyclo[2.1.1]hexane (24).** Ditosylamine **23** (1.15 g, 1.57 mmol) in anhydrous HMPA (7.8 mL) was treated with anhydrous potassium iodide (785 mg, 4.73 mmol) and anhydrous potassium acetate (465 mg, 4.73 mmol) at 120−130 °C for 5 days under N_2 atmosphere. After cooling to 0 °C, the reaction mixture was diluted with CH_2Cl_2. The organic layer was then washed with H_2O (90 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The orange residue was purified by column chromatography (silica gel, cyclohexane/EtOAc; 95/5 → 7/3) to yield acetate **24** (591 mg, 81%) as white crystals: mp 110−112 °C (Et_2O/CH_2Cl_2); IR (KBr) 1736, 1336, 1248, 1153 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.80 (m, 2H, arom), 7.41 (m, 2H, arom), 7.30 (m, 2H, arom), 7.27−7.19 (m, 3H, arom), 4.41 (m, 1H, H-1, J = 6.8 Hz), 3.95 (dd, 1H, H-7, J = 11.7, 7.2 Hz), 3.86 (dd, 1H, H-7′, J = 11.7, 6.8 Hz), 3.57 (d, 1H, H-3, J = 8.3 Hz), 3.48 (m, 1H, H-5), 3.45 (d, 1H, H-3′, J = 8.3 Hz), 2.93 (m, 1H, H-4, J = 6.8 Hz), 2.43 (s, 3H, CH_3), 2.30 (m, 1H, H-6, J = 7.2, 6.8 Hz), 2.00 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.7 (*C*═O), 143.2 (quat C, arom), 138.3 (quat C, arom), 133.4 (*C*H, arom), 129.5 (*C*H, arom), 129.1 (*C*H, arom), 127.4 (*C*H, arom), 126.8 (*C*H, arom), 67.3 (*C*H), 60.3 (*C*H_2), 48.4 (*C*H), 45.1 (*C*H_2), 44.8 (2 × *C*H), 21.5 (*C*H_3), 20.7 (*C*H_3); HRMS calcd for $C_{21}H_{23}NO_4SSe$ 465.0513, found 465.0532.

(1*R,4*S**,5*S**)-5-Acetoxymethyl-2-*N*-*p*-toluenesulfonyl-2-azabicyclo[2.1.1]hexane (25).** The reaction was run in the same experimental conditions as for **19** (except reaction time = 72 h) and starting from seleno compound **24** (583 mg, 1.25 mmol) in toluene (6.8 mL), *n*-Bu_3SnH (1.05 mL, 3.61 mmol), and a 0.02 M AIBN toluene solution (1.90 mL; 0.04 mmol). Bicyclo compound **25** (299 mg, 77%) was thus obtained as white crystals: mp 126−127 °C (Et_2O/CH_2Cl_2); IR (KBr) 1737, 1340, 1246, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.73 (d, 2H, arom, J = 8.2 Hz), 7.31 (d, 2H, arom, J = 8.2 Hz), 4.21 (ddd, 1H, H-1, J = 6.8, 1.9, 1.1 Hz), 3.98 (dd, 1H, H-7, J = 11.6, 7.0 Hz), 3.94 (dd, 1H, H-7′, J = 11.6, 6.8 Hz), 3.32 (d, 1H, H-3, J = 8.8 Hz), 3.15 (d, 1H, H-3′, J = 8.8 Hz), 2.69 (ddd, 1H, H-4, J = 6.8, 3.0, 2.8 Hz), 2.43 (s, 3H, CH_3), 2.28 (m, 1H, H-5, J = 7.0, 6.8, 3.0, 1.9 Hz), 2.02 (s, 3H, CH_3), 1.42 (ddd, 1H, H-6, J = 8.1, 2.8, 1.1 Hz), 0.68 (d, 1H, H-6′, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 171.0 (*C*═O), 143.6 (quat C, arom), 135.6 (quat C, arom), 129.8 (*C*H, arom), 127.7 (*C*H, arom), 63.6 (*C*H), 60.0 (*C*H_2), 47.1 (*C*H_2), 46.8 (*C*H), 39.6 (*C*H), 35.3 (*C*H_2), 21.5 (*C*H_3), 20.8 (*C*H_3). Anal. Calcd for $C_{15}H_{19}NO_4S{\cdot}0.2H_2O$: C, 57.56; H, 6.25; N, 4.47; S, 10.24. Found: C, 57.63; H, 6.21; N, 4.35; S, 10.15.

(1*R,4*S**,5*S**)-5-Hydroxymethyl-2-*N*-benzyloxycarbonyl-2-azabicyclo[2.1.1]hexane (4b).** A solution of **25** (75 mg, 0.24 mmol) in EtOAc (2 mL) was added in four portions over 2 h to a 32% solution of HBr in AcOH (3 mL) at 0 °C. Then the flask was sealed. After an additionnal 60 h of stirring at room temperature, the reaction mixture was cooled to 0 °C, and H_2O (6 mL) was added. The aqueous phase was washed with CH_2Cl_2 (2 × 3 mL) before being evaporated to dryness in vacuo to yield the corresponding crude amino alcohol hydrobromide (31 mg, 66%), which was purified via its benzyloxycarbonyl derivative **4b**. Amino alcohol hydrobromide (25 mg, 0.13 mmol) was added to a 1 M aqueous NaOH solution (260 μL, 0.26 mmol). After cooling to 0 °C, seven equal portions of (benzyloxy)carbonyl chloride (26 μL, 0.15 mmol) in dioxane (280 μL) were added to this solution, alternatively with seven

portions of 1 M aqueous NaOH (7 × 15 μL) over a 1 h period. The mixture was allowed to warm to room temperature over 3 h, stirred for an additional 16 h, and basified to pH 12 with NaOH. The mixture was stirred for 1 h and extracted with CH_2Cl_2 (3 × 4 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (silica gel, cyclohexane/EtOAc; 1/2) afforded hydroxy derivative **4b** (21 mg, 66% (44% from **25**)) as a colorless oil: IR (neat) 3406, 1693, 1425 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (m, 5H, arom), 5.16 (m, 2H, CH_2 benzylic), 4.42 (m, 1H, H-1), 3.28 (m, 4H, H-3 and H-7), 2.77 (m, 1H, H-4), 2.24 (m, 1H, H-5), 2.10 (br s, 1H, OH), 1.75 (m, 1H, H-6, J = 7.4 Hz), 1.35 (d, 1H, H-6′, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 156.7 (*C*═O), 136.8 (quat C, arom), 128.5 (*C*H, arom), 128.0 (*C*H, arom), 127.9 (*C*H, arom), 66.8 (CH_2), 61.1 and 60.7 (*C*H), 58.4 and 58.2 (CH_2), 50.0 and 49.6 (*C*H), 46.2 and 46.0 (CH_2), 39.2 and 38.9 (*C*H), 38.3 and 38.0 (CH_2); HRMS calcd for $C_{14}H_{17}NO_3$ 247.1208, found 247.1210.

(1*R,4*S**,5*S**)-2-*N*-Benzyloxycarbonyl-2-azabicyclo[2.1.1]-hexane-5-carboxylic Acid (26).** Alcohol **4b** (21 mg, 0.08 mmol) dissolved in acetone (0.6 mL) was added dropwise to a solution of freshly prepared Jones reagent (76 μL) in acetone (0.6 mL) at −5 °C over a period of 2 h. The reaction mixture was stirred at room temperature for 4 h, and then *i*PrOH (10 μL) was added at 0 °C. The mixture was filtered through Celite and washed with acetone (2 mL). The solvent was evaporated in vacuo, and the residue was dissolved in CH_2Cl_2 and extracted with a 1 M aqueous NaOH (3 mL). The basic aqueous layer was then acidified with concentrated H_2SO_4 (pH 1−2) and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic layers were dried over $MgSO_4$, and evaporation of the solvent provided carboxylic acid **26** (18 mg, 82%) as white crystals. It was pure enough to be used as such in the next step: mp 97−99 °C; IR (KBr) 3442, 1705, 1674, 1436 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.10 (br s, 1H, CO_2H), 7.30 (m, 5H, arom), 5.15 (m, 2H, CH_2 benzylic), 4.68 (m, 1H, H-1), 3.67 (m, 1H, H-3, J = 8.9 Hz), 3.36 (d, 1H, H-3′, J = 8.9 Hz), 3.09 (m, 1H, H-4), 2.84 (m, 1H, H-5), 1.82 (m, 1H, H-6, J = 7.8 Hz), 1.35 (d, 1H, H-6′, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 172.9 (*C*═O), 156.6 (*C*═O), 136.7 (quat C, arom), 128.4 (*C*H, arom), 127.9 (*C*H, arom), 127.8 (*C*H, arom), 66.9 (CH_2), 62.2 (*C*H), 50.0 (*C*H), 46.7 (CH_2), 41.0 (*C*H), 37.9 (CH_2); HRMS calcd for $C_{14}H_{15}NO_4$ 261.1001, found 261.0998.

(1*R,4*S**,5*S**)-2-Azabicyclo[2.1.1]hexane-5-carboxylic Acid (4c).** A suspension of compound **26** (12 mg, 0.05 mmol) and 10% Pd/C (12 mg) in MeOH (7 mL) was stirred for 12 h under H_2 (1 atm) at room temperature. The palladium carbon catalyst was then filtered off, washed with H_2O (2 mL), and the solution was concentrated in vacuo to give β-amino acid **4c** (6 mg, 100%) as a pale yellow oil: IR (neat) 3452, 1578, 1419 cm^{-1}; ^1H NMR (D_2O) δ 4.15 (m, 1H, H-1, J = 5.9 Hz), 3.27 (d, 1H, H-3, J = 10.3 Hz), 3.21 (d, 1H, H-3′, J = 10.3 Hz), 3.03 (m, 1H, H-4, J = 5.9 Hz), 2.89 (m, 1H, H-5), 1.87 (m, 1H, H-6, J = 9.0 Hz), 1.24 (d, 1H, H-6′, J = 9.0 Hz); ^{13}C NMR (D_2O) δ 176.2 (*C*═O), 61.0 (*C*H), 50.9 (*C*H), 46.4 (CH_2), 41.4 (*C*H), 33.8 (CH_2); HRMS calcd for $[(C_6H_9NO_2) + H]^+$ 128.0712, found 128.0709.

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Supporting Information Available: ^1H NMR spectra of **4a**, **4b**, **4c**, **14**, **15**, **20**, **24**, **26** and phase-sensitive NOESY spectra of **17a** and **17b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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