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The regioselectivity of the addition of benzeneselenyl chloride to 7-azanorborn-5-ene-2-yl derivatives is controlled by the 2-substituent: new entry into 3- and 4-hydroxy-5-substituted prolines

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ABSTRACT

The electrophilic addition of benzeneselenyl chloride to the alkene moiety of 7-azabicyclo[2.2.1]hept-5-en-2-yl derivatives has been studied. With camphanates **8** and **9** *N*-Boc-5-*endo*-chloro-6-*exo*-phenylseleno-7-azanorborn-2-yl camphanates **10** and **11** are obtained with high regioselectivity due to a steric control. With *N*-Boc-7-azanorbor-5-en-2-one (**2**) the corresponding 6-*endo*-chloro-5-*exo*-phenylseleno derivative **15** is obtained in high yield due to a kinetic control attributed to the electron-releasing ability of the homoconjugated carbonyl group. Bicyclic adducts **10** and **11** and **15** are readily converted into 4-hydroxy-(**14**) and 3-hydroxy-5-substituted proline derivatives **19**, respectively.

1. Introduction

The 'naked sugar' methodology transforms furan into enantiomerically pure bicyclic derivatives such as 7-oxanorborn-5-en-2-one (**1** and *ent*-**1**) that are synthetic precursors for a large variety of natural products, carbohydrates, and analogues of biological interest.[1] We now intend to extend this methodology to the synthesis of further products of interest, such as proline analogues and dideoxyiminoalditols and derivatives starting from *N*-Boc protected 7-aza derivatives, such as **2** ('naked aza-sugar'). Interest in the chemistry of 7-azabicyclo[2.2.1]heptane systems has increased since 1992, especially due to the biological relevance of Epibatidine,[2] a natural alkaloid containing a 7-azabicyclo[2.2.1]heptane skeleton and which is a potent non-opioid analgesic. Thus, compounds containing the 7-azabicyclo[2.2.1]heptane system have become popular synthetic targets (Fig. 1).[3]

On their side hydroxylated prolines have been shown to significantly influence polypeptide secondary structure in antibiotics.[4] Dihydroxyprolines are present in adhesive proteins produced by marine organisms.[4b,5] Properties of peptides, and especially their water solubility, are modified by their degree of hydroxylation. Bulgecinine is a 4-hydroxy-5-hydroxymethylproline present in Bulgecins A, B, and C, which are natural glycopeptide antibiotics.[6] Incorporation of 3- or 4-hydroxyproline and of 3,4-dihydroxyproline moieties into fucopeptides and thiofucopeptides, that are mimics of the structure of sialyl Lewis X, increases interaction with E- and P-selectins.[7] This has stimulated the synthesis of polyhydroxylated proline derivatives.[8]

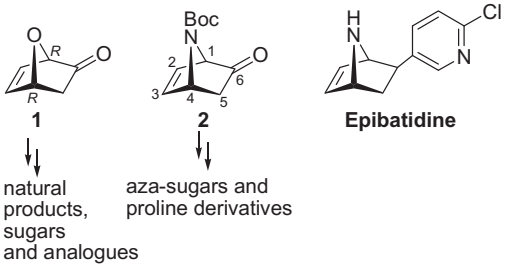

Figure 1.

As part of our studies on the chemistry of 7-azabicyclo[2.2.1]heptanes[9] and their use in the synthesis of polyfunctional prolines,[10]

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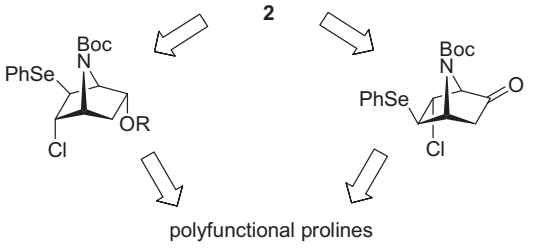
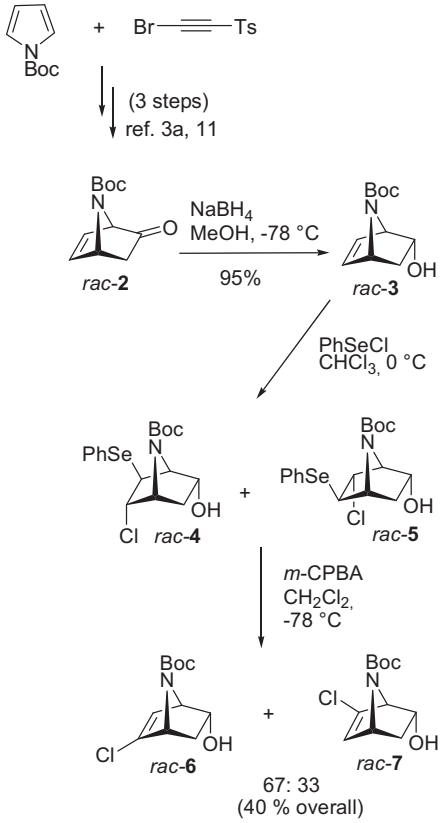
we report herein the development of synthetic routes toward 3- and 4-hydroxy-5-substituted-prolines based on the functionalization of 7-azabicyclo[2.2.1]hept-5-en-2-one **2** (Scheme 1).



Scheme 1.

2. Results and discussion

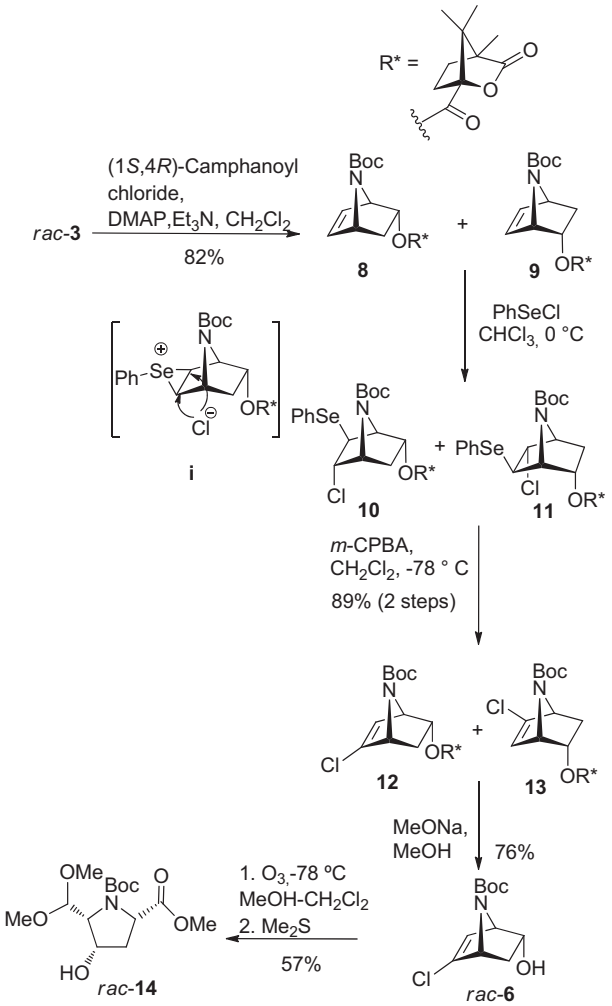
Racemic ketone **2** was prepared in three steps from *N*-Boc-pyrrole and 2-bromoethynyl *p*-tolyl sulfone according a procedure reported by Trudell and co-workers[3a] and subsequently improved by Kozikowski and co-workers.[11] Reduction of **2** with $NaBH_4$ at low temperature afforded the *endo*-alcohol **3** in 95% yield as unique stereoisomer (Scheme 2).



Scheme 2. Electrophilic addition of benzeneselenyl chloride to *N*-Boc-7-azabicyclo-[2.2.1]hept-5-en-2-ol **3**.

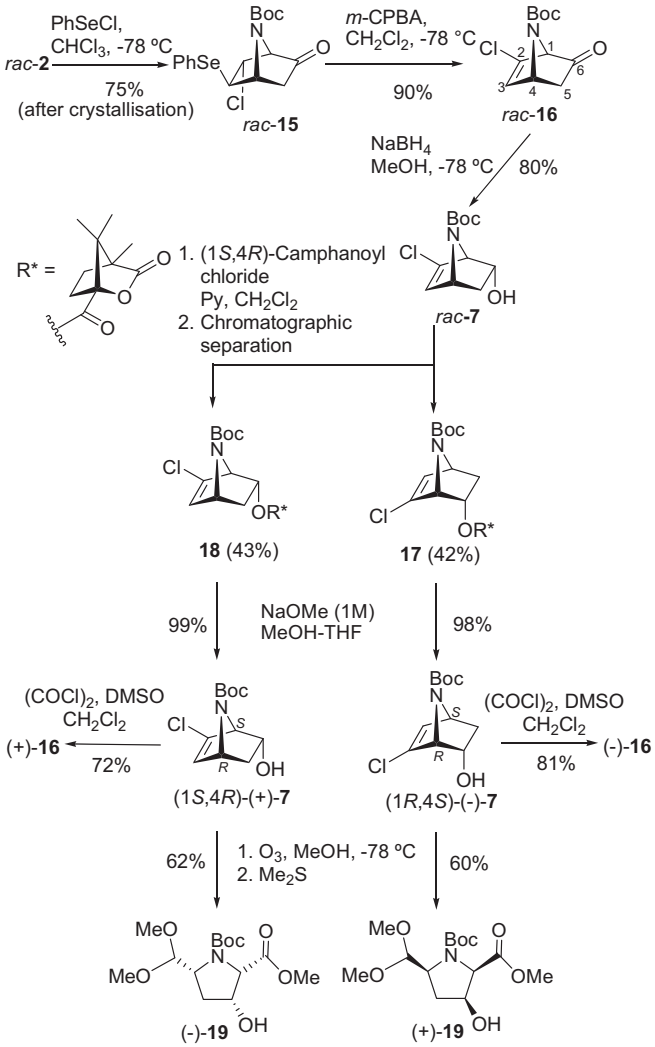
Electrophilic addition of benzeneselenyl chloride to the alkene moiety of **3** led to a mixture of adducts **4** and **5** that were directly subjected to an oxidative treatment with *m*-CPBA to afford a mixture of regioisomeric chloroalkenes **6** and **7** in 40% overall yield (ratio **6**/**7**=67/33). Plumet and co-workers reported a similar electrophilic addition on the oxa-analogue of compound **3**[12] at −78 °C that afforded a mixture of the oxa-analogue of **4** and an oxetane derivative arising from intramolecular quenching of the bridged selenonium cation intermediate by the 2-*endo*-hydroxyl group. With the aza analogue **3** such oxetane formation was not observed.

The influence of the nature of *endo*-substituent at C-2 of the bicyclic skeleton on the regioselectivity of the addition was evidenced by esterification of the racemic 2-*endo*-alcohol **3** with (1*S*,4*R*)-camphanoyl chloride. This produced (Scheme 3) a mixture of two diastereoisomeric camphanoyl esters **8** and **9** that could not be separated. Electrophilic addition of benzeneselenyl chloride to this mixture gave a 1:1 mixture of adducts **10** and **11**. Oxidative elimination of the phenylseleno group induced by *m*-CPBA from adducts **10** and **11** afforded a 1:1 mixture of diastereoisomeric alkenyl chlorides **12** and **13** in good overall yield. In this case, the regioselectivity of the electrophilic addition was controlled by the steric bulk of the 2-*endo*-substituent, which empedes chloride anion attack onto the 6-*endo* position of the intermediate bridged cation (**i**). Unfortunately, diastereoisomers **12** and **13** could not be separated. Methanolysis of the mixture of **12** and **13** afforded pure racemic vinyl chloride **6** (see Scheme 3), thus demonstrating the high regioselectivity of the addition of PhSeCl to camphanates **8** and **9**. Thus ozonolysis of this mixture followed by an reductive work-up afforded racemic methyl all-*cis*-*N*-Boc-4-hydroxy-5-(dimethoxymethyl)prolinate (**14**) in good overall yield after spontaneous formation of the dimethylacetal function.



Scheme 3. Influence of bulky 2-*endo*-substituent on the regioselectivity of the electrophilic addition of benzeneselenyl chloride to 7-azanorbornene derivatives.

The stereo- and regioselectivity of the electrophilic addition of benzeneselenyl chloride to racemic ketone **2** was also studied (Scheme 4). Under kinetically controlled conditions (−78 °C, no competitive elimination) the addition of PhSeCl afforded a single adduct **15** (by ^{1}H NMR) that was isolated in 75% yield after crystallization. Its ^{1}H NMR spectrum displayed typical coupling constants for 5-H and 6-H ($J_{1,6}$=5 Hz, $J_{4,5}$=0 Hz) that were in agreement with those of the 7-oxa analogue previously reported.[13] Furthermore, the structure of **15** was unambiguously confirmed by X-ray diffraction of a single crystal (Fig. 2).[14] According to previous results with 7-carba- and 7-oxa-analogues,[13,15] the electron-releasing homoconjugated carbonyl group plays a crucial role on the regioselectivity of the electrophilic addition of the bicyclic alkene because of the frangomeric effect (n(CO)/σ/2p$^+$ hyperconjugative interaction) (Scheme 5), as supported by high level quantum calculations.[16]



Scheme 4. Regio- and stereoselective electrophilic addition of benzeneselenyl chloride to *N*-Boc-7-azabicyclo[2.2.1]hept-5-en-2-one (**2**).

Oxidative deselenation of **15** (Scheme 4) afforded the alkenyl chloride **16** in 90% yield. Stereoselective reduction of the ketone group in **16** with $NaBH_4$ at −78 °C provided pure **7** isolated in 80% yield. Optical resolution of this racemic mixture was carried out by formation of diastereoisomeric esters employing (−)-(1*S*,4*R*)-camphanic acid chloride as a resolving agent. Diastereoisomeric esters **17** and **18** were readily separated by flash column chromatography on silica gel. Removal of the chiral auxiliary from **17** and **18** was realized by treating these compounds with a catalytic amount of NaOMe in MeOH/THF. This afforded the enantiomerically pure

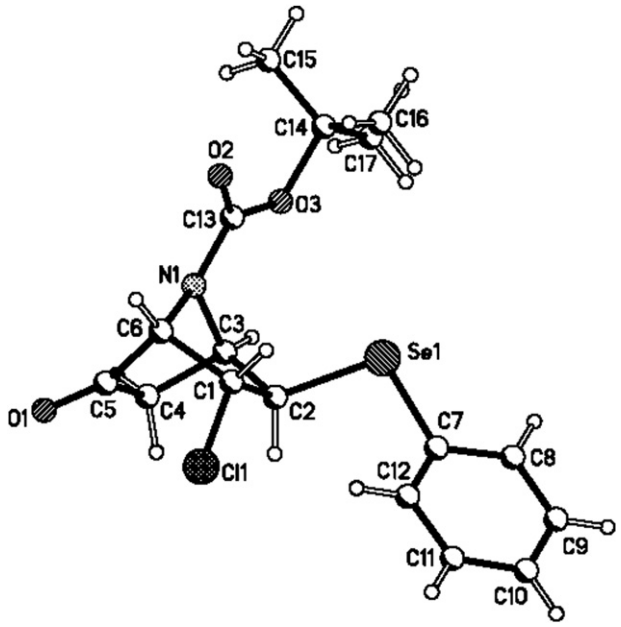
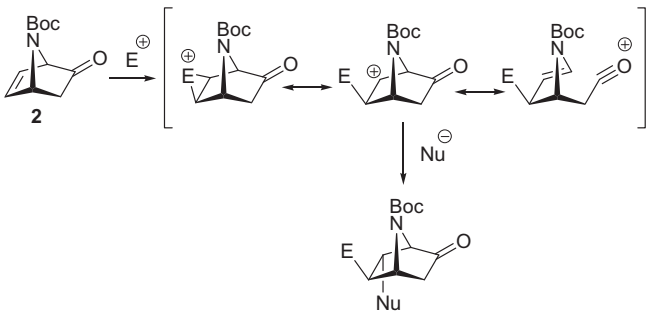


Figure 2. X-Ray diffraction analysis of **15**.



Scheme 5. Effect of the electron-releasing homoconjugated carbonyl on the electrophilic addition to 7-azanorborn-5-en-2-one derivatives.

alcohols (−)-**7** ($[\alpha]_D^{25}$ −74.6 (*c* 0.24, $CHCl_3$)) and (+)-**7** ($[\alpha]_D^{25}$ +72.5 (*c* 0.24, $CHCl_3$)), respectively. Cleavage of the bicyclic skeleton in (−)-**7** was carried out by ozonolysis, followed by treatment with dimethyl sulfide. This afforded the methyl 3-hydroxy-5-substituted-prolinate derivative (+)-**19** in 62% overall yield after spontaneous formation of the dimethylacetal function. The same procedure was used for the synthesis of (−)-**19** from (+)-**7**.

Additionally, Swern oxidation of alcohols (1*R*,4*S*)-(−)-**7** and (1*S*,4*R*)-(+)-**7** afforded enantiomerically pure ketones (1*R*,4*S*)-(−)-**16** and (1*S*,4*R*)-(+)-**16**, respectively. The assignment of the absolute configuration of (+)-**16** and (−)-**16**, and therefore of proline derivatives (+)-**19** and (−)-**19**, was realized by their CD spectral correlation with known enantiomerically pure analogue ketones. CD spectrum of enone (−)-**16** shows a negative Cotton effect at λ=304 nm for its $n\rightarrow\pi^*_{CO}$ transition (Fig. 3). Similar negative Cotton effect has been observed for the $n\rightarrow\pi^*_{CO}$ transitions of (1*S*,4*S*)-(−)-(*N*-*tert*-butoxycarbonyl)-7-azabicyclo[2.2.1]hept-5-en-2-one 1,[9b] (1*S*,4*S*)-(−)-7-oxabicyclo[2.2.1]hept-5-en-2-one 1[17] and (1*S*,4*S*)-(−)-bicyclo[2.2.2]oct-5-en-2-one.[17] The CD spectra of these three latter enones show an 'extra' negative Cotton effect between λ 205 and 215 nm associated with a mixed transition resulting from through-space (π(alkene)$\rightarrow\pi^*_{CO}$) and through-bond (n(CO)$\rightarrow\sigma\rightarrow\pi^*$(alkene)) interactions. In the case of ketone (−)-**16** we have observed a positive Cotton effect at λ=194 nm. The surprise, nevertheless, is the observation of a third negative Cotton effect at λ=239 nm seen only for enones (−)-**2** and (−)-**16** and not for the

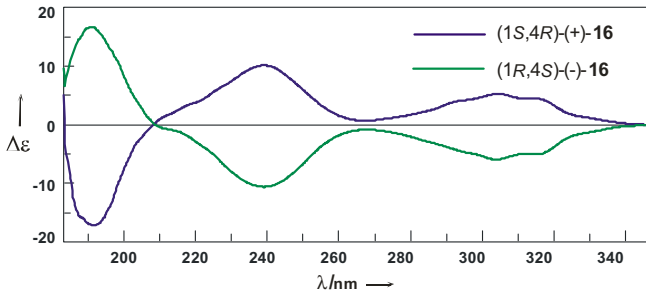


Figure 3. CD spectra of (1*S*,4*R*)-(+)-16 (0.00091 M^{-1}) and (1*R*,4*S*)-(−)-16 (0.00094 M^{-1}) in CH_3CN.

other analogues. This suggests that the 7-(*tert*-butoxycarbonyl)aza bridge introduces further electronic interaction between the chromophores of (−)-**2** and (−)-**16**. This is also indicated by the UV absorption spectrum of (−)-**2** (Fig. 4). For compound (1*S*,4*R*)-(+)-**16** all observed Cotton effects have opposite sign (Fig. 3). The UV absorption spectra of (−)-**16** and its enantiomer are also shown (Fig. 4).

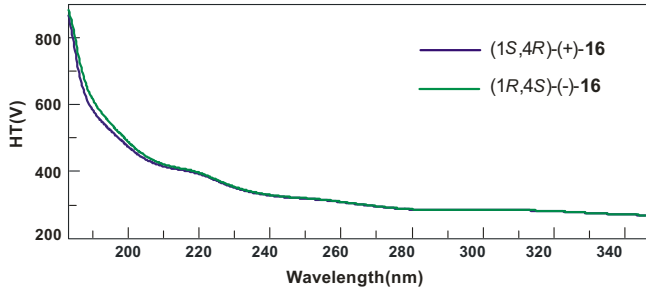


Figure 4. UV absorption spectra of (1*S*,4*R*)-(+)-16 (0.00091 M^{-1}) and (1*R*,4*S*)-(−)-16 (0.00094 M^{-1}) in CH_3CN.

3. Conclusion

Benzeneselenyl chloride adds to the alkene moiety of 7-aza-norborn-5-en-2-yl derivatives **2**, **8**, and **9** with high stereo- and regioselectivity. These additions are controlled by the nature of the remote substituent at C(2). The resulting chloro-phenylseleno adducts are transformed in few steps into the 4- and 3-hydroxy-5-substituted proline derivatives **14** and **19**. In the case of modified prolines **19**, the route allowed the preparation of both enantiomerically pure forms. The absolute configuration of (+)-**19** and (−)-**19** was assigned.

4. Experimental section

4.1. General

All commercially available reagents (Fluka, Aldrich, Acros Organics) were used without further purification. Solvents were dried by standard methods. Light petroleum ether used refers to the fraction boiling between 40–60 °C. Liquid/solid flash chromatography (FC): silica gel 60 (Merck No. 9385, 240–400 mesh). TLC (reaction monitoring): Merck silica gel 60 F_{254} plates; detection by UV light, Pancaldi reagent ($(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O), 1% $KMnO_4$ in H_2O or 1% ninhydrin in MeOH. IR Spectra: Perkin–Elmer 1420 spectrometer; in cm^{-1}. Optical rotations: at 25 °C; Jasco P-1020 polarimeter: $[\alpha]_D$ in 10^{-1} deg cm^2 g^{-1}. ^1H NMR spectra: Bruker ARX-400 spectrometer (400 MHz); δ(H) in parts per million rel to the solvent's residual ^1H signal ($CDCl_3$, δ(H) 7.27; CD_3OD, δ(H) 3.31; C_6D_6, δ(H) 7.30) as internal reference; ^1H assignments were confirmed by 2D-COSY-45 experiment. ^{13}C NMR spectra: same instrument as for ^1H (100.6 MHz); δ(H) in ppm rel to the solvent's C-signal ($CDCl_3$, δ(C) 77.0; CD_3OD, δ(C) 49.0; C_6D_6, δ(H) 128.0) as internal reference; ^{13}C assignments were confirmed by 2D-HMQC; coupling constants *J* in hertz. MS: Nermag R 10-10*C*, chemical-ionization (NH_3) mode; *m*/*z* (% rel to the base peak (=100%)). UV measurements were made on a Cary 100 spectrophotometer in acetonitrile (for UV-spectroscopy, Fluka). CD spectra were measured 25°C rt in acetonitrile (for UV-spectroscopy, Fluka) on a Jasco 715 spectrophotometer by using cells with path length 0.1 to 1 cm (spectral band width 2 nm), sensitivity 5×10^{-6} or 10×10^{-6} [ΔA-unit nm^{-1}], where $\Delta A=A_L-A_R$ is the difference in the absorbance. $\Delta\epsilon$ is expressed in [LM^{-1} cm^{-1}]. Elemental analyses: Ilse Beetz, D-96301 Kronach, Germany. Melting points: BUCHI SMP-20 apparatus and are uncorrected.

*4.1.1. 7-(tert-Butoxycarbonyl)-7-azabicyclo[2.2.1]hept-5-en-2-endo-ol (rac-**3**).* $NaBH_4$ (0.155 g, 4.11 mmol) was added portionwise to a stirred solution of **2** (0.43 g, 2.05 mmol) in MeOH (15 mL) cooled to −78 °C. After stirring at −78 °C for 30 min and 2 h at rt, AcOH (0.3 mL) was added dropwise. Subsequently, CH_2C1_2 (15 mL) was added and the solution was washed with H_2O and brine. After drying ($MgSO_4$), the solvent was evaporated affording *rac*-**3** (0.41 g, 95%) as a white solid. Elem. Anal. Calcd for $C_{11}H_{17}NO_3$ (211.25): C, 62.54; H, 8.11; N, 6.63; found: C, 62.66; H, 8.12; N, 6.66. Mp=111–112 °C. IR (KBr): 3405, 1680, 1455, 1370, 1280, 1260, 1165, 1085, 1070, 880 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 322 K): δ 6.54 (dd, 1H, $J_{5,4}$=5.6, $J_{5,6}$=1.7, H-5), 6.28 (dd, 1H, $J_{6,1}$=5.6, H-6), 4.65 (br s, 1H, H-1), 4.58 (br s, 1H, H-4), 4.46 (ddd, 1H, $J_{2exo,3}$=7.3, $J_{2exo,1}$=4, H-2), 2.3 (ddd, 1H, $J_{3exo,3endo}$=12.4, $J_{3,2exo}$=7.3, $J_{3,4}$=4.3, H-3*exo*), 1.4 (s, 9H, $(CH_3)_3C$), 0.86 (dd, 1H, $J_{3endo,3exo}$=12.4, $J_{2exo,3}$=7.3, H-3*endo*). ^{13}C NMR (101.61 MHz, $CDCl_3$, 322 K): δ 155.1 ($COC(CH_3)_3$), 138.4 (C-5), 131.4 (C-6), 80.1 ($C(CH_3)_3$), 68.9 (C-2), 63.0 (C-1), 61.0 (C-4), 36.5 (C-3), 28.1 ($(CH_3)_3$).

*4.1.2. (±)-7-(tert-Butoxycarbonyl)-5-chloro-7-azabicyclo[2.2.1]hept-5-en-2-endo-ol (rac-**6**).* Method (a): A solution of racemic alcohol *rac*-**3** (0.34 g, 0.18 mmol) in $CHC1_3$ (4 mL) was cooled to −78 °C and stirred under an atmosphere of argon while a solution of PhSeCl (0.034 g, 0.18 mmol) in $CHC1_3$ (2 mL) was added dropwise over 15 min. The reaction mixture was stirred for an additional 30 min at 0 °C and then overnight at rt. The resulting solution was diluted with $CHC1_3$ (40 mL) and successively washed with 5% aq Na_2CO_3 (10 mL), H_2O (10 mL), and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated to give a crude of the products **4** and **5** that was used in the following step without purification. To a solution of the resulting crude of **4** and **5** (0.18 mmol) in CH_2C1_2 (3 mL), stirred at −78 °C under an atmosphere of argon, a solution of *m*-CPBA (0.045 g, 0.18 mmol) in CH_2C1_2 (3 mL) was added dropwise over 30 min. The solution was stirred at −78 °C for 2 h before being warmed to 20 °C, and then was stirred for additional 10 h. Subsequently, the mixture was diluted with CH_2Cl_2 (20 mL) and washed with 5% aq Na_2CO_3 (7 mL), H_2O (7 mL), and brine (7 mL). The organic extract was dried ($MgSO_4$), filtered, and concentrated to give an orange oil that was subjected to column chromatography (EtOAc/petroleum ether, 2:3 v/v), to afford a mixture of *rac*-**6** and *rac*-**7** (0.018 g, 40%) that could not be separated.

Method (b): To a solution of **12** and **13** (0.1 g, 0.23 mmol) in anhydrous MeOH/THF (14 mL, 6:1 v/v), was added MeONa/MeOH 1 M (catalytic) and then reaction mixture was stirred for 2 h. Subsequently, the mixture was concentrated and purified by column chromatography on silica gel (AcOEt/petroleum ether, 2:3 v/v), to afford *rac*-**6** (0.043 g, 76%) as a white solid. Elem. Anal. Calcd for $C_{11}H_{16}NClO_3$ (245.70): C, 53.77; H, 6.56; N, 5.70; found: C, 53.90; H,

6.61; N, 5.63. ^{1}H NMR (300 MHz, $CDCl_3$, 318 K): δ 6.17 (s, 1H, H-6), 4.70 (br s, 1H, H-1), 4.6 (br s, 1H, H-2*exo*), 4.46 (d, $J_{3exo,\ 4}$=3.9, 1H, H-4), 2.42 (ddd, 2H, $J_{3exo,3endo}$=12.2, $J_{3exo,\ 2exo}$=7.8, $J_{3exo,\ 4}$=4, H-3*exo*), 1.44 (s, 9H, (CH_3)$_3$C), 1.12 (dd, 1H, $J_{3exo,3endo}$=12.2, $J_{3endo,2exo}$=2.5, H-3*endo*). ^{13}C NMR (75.4 MHz, $CDCl_3$, 318 K) δ 154.8 (COC(CH_3)$_3$), 82.1 (C(CH_3)$_3$), 126.4 (C-6), 80.7 (C(CH_3)$_3$), 70.9 (C-2), 65.9 (C-4), 64.7 (C-1), 36.7 (C-3), 28.1 ((CH$_3$)$_3$).

*4.1.3. (±)-7-(tert-Butoxycarbonyl)-2-chloro-7-azabicyclo[2.2.1]hept-5-en-6-endo-ol (rac-**7**).* Method (a): This compound was obtained as a mixture *rac*-**6**+*rac*-**7** (66:33, 40%) following the procedure described for **6** (method a).

Method (b): $NaBH_4$ (0.178 g, 4.51 mmol) was added portionwise to a stirred solution of *rac*-**15** (0.55 g, 2.25 mmol) in MeOH (10 mL) cooled to −78 °C. After stirring at −78 °C for 30 min, AcOH (0.1 mL) was added dropwise. Subsequently, CH_2C1_2 was added and the solution was washed with H_2O and brine. After drying ($MgSO_4$), the solvent was evaporated to afford *rac*-**7** (0.44 g, 80%), as white crystals. CIMS *m*/*z* 246 [4%, (M+H)$^+$]. EI-HRMS (*m*/*z*) calcd for $C_{11}H_{17}NO_3Cl$ 246.0986, found 246.0986. ^{1}H NMR (400 MHz, $CDCl_3$, 320 K): δ 6.35 (d, 1H, *J*=2.4, H-3), 4.67–4.60 (m, 2H, H-6, H-4), 4.56 (d, 1H, *J*=4.0, H-1), 2.39 (ddd, 1H, *J*=12.1, 7.7, 4.3, H-5*exo*), 1.43 (s, 9H, (CH_3)$_3$C), 1.06 (dd, 1H, *J*=12.1, 2.3, H-3*endo*). ^{13}C NMR (100.6 MHz, $CDCl_3$, 320 K): δ 154.9 (*C*O of Boc), 135.6 (C-2), 131.6 (C-3), 80.9 ((CH_3)$_3$*C*), 69.3 (C-6), 68.0 (C-1), 62.1 (C-4), 36.2 (C-5), 28.2 ((CH$_3$)$_3$C).

*4.1.4. Mixture of (1R,4R) and (1S,4S)-7-tert-butoxycarbonyl-2-endo-[(1S,4R)-camphanoyloxy]-7-azabicyclo[2.2.1]hept-5-ene (**8** and **9**).* To a cold (0 °C) solution of *rac*-**3** (0.24 g, 1.13 mmol) in anhydrous CH_2Cl_2 (8 mL) were added Et_3N (0.32 mL, 2.27 mmol), (1*S*,4*R*)-(−)-camphanic acid chloride (0.5 g, 2.27 mmol), and a catalytic amount of DMAP. After stirring for 12 h at rt, a satd aq solution of citric acid was added and the mixture was extracted with CH_2Cl_2 (2×). The combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure, and purified by column chromatography on silica gel (light petroleum ether/AcOEt, 2:1 v/v) to give a mixture of **8** and **9** (0.36 g, 82% yield) as a white solid. Elem. Anal. Calcd for $C_{21}H_{29}NO_6$ (391.45): C, 64.43; H, 7.47; N, 3.58; found: C, 64.32; H, 7.64; N, 3.66. MALDI-HRMS (*m*/*z*) calcd for $C_{21}H_{29}NO_6K$ 430.1632, found 430.1623. IR (KBr): 2960, 1790, 1700, 1450, 1365, 1265, 1165, 1100, 1065 cm^{-1}. Mp=115–117 °C. ^{1}H NMR (mixture of stereoisomers, 400 MHz, C_6D_6, 335 K): δ 6.12 (dd, 1H, $J_{5,4}$=5.7, $J_{5,6'}$=1.2, H-5), 5.98 (m, 1H, H-6), 5.26–5.21 (m, 1H, H-2), 5.00 (br s, 1H, H-1), 4.51 (br s, 1H, H-4), 2.19 (ddd, 2H, $J_{3exo,3endo}$=12.3, $J_{3exo,2exo}$=8, $J_{3exo,4}$=4.3, H-3*exo*), 2.02–1.98 (m, 1H, H-6a′), 1.73–1.75 (m, 1H, H-6b′), 1.47 (m, 9H, (CH_3)$_3$C), 1.37–1.25 (m, 2H, H-6a and 3-*endo*), 1.04, 0.95, 0.94, 0.81 (4s, 18H, CH_3). For **8**: ^{13}C NMR (101.61 MHz, C_6D_6, 335 K): δ 176.6 (CO of ester), 167.0 (C-3′), 154.5 (CO of carbamate), 138.2 (C-5), 131.4 (C-6), 91.3 (C-1′), 79.5 (C(CH_3)$_3$), 72.1 (C-2), 61.5 (C-1), 60.7 (C-4), 54.3 (C-4′), 53.4 (C-7′), 34.0 (C-3), 30.6, 28.6 (C-5′, C-6′), 27.9 ((CH_3)$_3$), 16.5, 16.2, 9.3 (3 CH_3 of camph.). For **9**: ^{13}C NMR (101.61 MHz, C_6D_6, 335 K): δ 176.6 (*C*O of ester), 167.0 (C-3′), 154.5 (*C*O of carbamate), 138.2 (C-5), 131.4 (C-6), 90.1 (C-1′), 79.7 (C(CH_3)$_3$), 72.1 (C-2), 61.6 (C-1), 60.7 (C-4), 54.3 (C-4′), 53.5 (C-7′), 34.0 (C-3), 30.6, 28.7 (C-5′, C-6′), 27.9 ((CH_3)$_3$), 16.4, 16.1, 9.3 (3 CH_3 of camph.).

*4.1.5. Mixture of (1R,4R) and (1S,4S)-2-endo-[(1S,4R)-camphanoyloxy]-5-chloro-7-(tert-butoxycarbonyl)-7-azabicyclo[2.2.1]hept-5-ene (**12** and **13**).* A mixture of **8** and **9** (0.266 g, 0.68 mmol) in $CHCl_3$ (4 mL) was cooled to −60 °C and stirred under an atmosphere of argon while a solution of PhSeCl (0.148 g, 0.78 mmol) in $CHC1_3$ (2 mL) was added dropwise for 15 min. The solution was stirred for an additional 30 min at −60 °C and then overnight at rt. After complete disappearance of **8**/**9**, the orange solution was diluted with $CHCl_3$ and poured into a 5% aq Na_2CO_3. The organic phase was collected, washed with brine, dried ($MgSO_4$), filtered, and evaporated to give a crude mixture of **10** and **11**. A solution of *m*-CPBA (0.121 g, 0.68 mmol) in CH_2C1_2 (2 mL) was added dropwise to this crude mixture of **10** and **11** (0.68 mmol) dissolved in CH_2C1_2 (4 mL) over 30 min. The resulting mixture was allowed to reach +5 °C in 1 h and stirred at this temperature for additional 30 min. Then it was poured into 5% aq Na_2CO_3 and aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to give a yellow solid. Purification by column chromatography (EtOAc/petroleum ether, 1:3 v/v), afforded **12** and **13** (1:1 mixture, 0.337 g, 89%) as a white solid. MALDI-HRMS (*m*/*z*), calcd for $C_{21}H_{28}ClNO_6Na$ 448.1503, found: 448.1590. IR (KBr): 2970, 1790, 1750, 1710, 1450, 1315, 1265, 1165, 1065, 1020 cm^{-1}. ^{1}H NMR (mixture of two stereoisomers, 400 MHz, C_6D_6, 335 K): δ 5.80 (s, 1H, H-6), 5.21–5.13 (m, 1H, H-2), 4.90 (br s, 1H, H-1), 4.42 (br s, 1H, H-4), 2.19 (ddd, 2H, $J_{3exo,3endo}$=12. 3, $J_{3exo,2}$=7.7, $J_{3exo,4}$=3.9, H-3*exo*), 2.02–1.81 (m, 1H, H-6a′), 1.66–1.57 (m, 1H, H-6b′), 1.33 (m, 9H, (CH_3)$_3$C), 1.28–1.22 (m, 2H, H-6a), 1.09 (dd, 1H, $J_{3exo,3endo}$=12.3, $J_{3endo,2}$=2.4, H-3*endo*), 0.84, 0.74, 0.73, 0.62 (4s, 18H, CH_3). ^{13}C NMR (101.61, MHz, $CDCl_3$, 320 K, mixture of two stereoisomers, selected carbon peaks): δ 177.5, 177.4, 167.8, 166.8 (OCO, C(3) of camph.), 154.0 (COC(CH_3)$_3$), 134.6, 134.2 (C-arom), 129.4 (C-arom), 129.0 (C-arom), 128.2, 128.1 (C-arom), 90.7 (C-1 of camph.), 81.5 ((CH_3)$_3$*C*), 73.8, 73.6 (C-6), 65.1 (C-1), 63.3 (C-3), 61.6 (C-4), 54.9, 54.8, 54.1, 54.0 (C-7, C-4 of camph.), 46.1, 45.9 (C-2), 30.74, 30.69 (C-6 of camph.), 29.5, 29.4 (C-5), 29.0, 28.9 (C-5 of camph.), 28.3 ((CH_3)$_3$C), 16.9, 16.8, 16.6 (2 *C*H$_3$–C(7) of camph.), 9.6, 9.5 (*C*H$_3$–C(4) of camph.).

*4.1.6. (±)-(2SR,4RS,5RS)-N-(tert-Butoxycarbonyl)-5-dimethoxymethyl-4-hydroxy-2-methoxycarbonylpyrrolidine (rac-**14**).* O_3, in O_2 was bubbled through a solution of **6** (0.067 g, 0.27 mmol) in anhydrous MeOH (10 mL) cooled to −78 °C until persistence of the blue color. O_2 was bubbled through the solution to eliminate the excess of O_3. After addition of Me_2S (0.5 mL), the mixture was allowed to warm up to 20 °C and was stirred for 6 h. Solid $NaHCO_3$ was added until pH=7 and the solvent evaporated. Subsequently, the residue was dissolved in CH_2C1_2 and the solution washed with H_2O (2×). The aqueous layers were combined and re-extracted with CH_2C1_2. The organic layers were combined, washed with brine, dried ($MgSO_4$), and evaporated. The crude was purified by column chromatography on silica gel (CH_2Cl_2→CH_2Cl_2/MeOH 75/1 v/v) to give *rac*-**14** (0.05 g, 57%) as a white solid. CIMS (NH_3): 337 (6, [M+NH_4]$^+$), 320 (41, [M+H]$^+$), 319 (25, [M]$^+$). ESI-HRMS (*m*/*z*) calcd for $C_{14}H_{25}NO_7Na$ 342.1528, found: 342.1531. IR (film): 3480, 2953, 1756, 1697, 1438, 1389, 1365, 1160, 1080, 907, 761 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 315 K): δ 4.87 (br s, 1H, C*H*(OMe)$_2$), 4.43 (m, 1H, H-4), 4.27 (dd, 1H, *J*=7.9, 7.9, H-2), 3.95 (dd, 1H, *J*=6.7, 2.9, H–C(5)), 3.74 (*s*, 3H, OCH_3), 3.59 (*s*, 3H, OCH_3), 3.54 (*s*, 3H, OCH_3), 2.41 (ddd, 1H, *J*=14.0, 8.2, *J*=6.6, H–C(3a)), 2.19 (dt, 1H, *J*=14.0, *J*=7.8, H–C(3b)), 1.46 (*s*, 9H, (CH_3)$_3$C). ^{13}C NMR (100.6 MHz, $CDCl_3$, 315 K): δ 172.6 (*C*OOMe), 154.3 (*C*O of Boc), 107.5 (*C*H(OMe)$_2$), 80.7 (C(CH_3)$_3$), 71.7 (C-4), 60.7 (C-5), 58.2 (OCH_3), 57.8 (C-2), 56.8 (OCH_3), 51.8 (OCH_3), 37.7 (C-3), 28.2 ((CH_3)$_3$C).

*4.1.7. (±)-5-exo-Benzeneselenenyl-6-endo-chloro-7-(tert-butoxycarbonyl)-7-azabicyclo[2.2.1]heptan-2-one (rac-**15**).* A solution of racemic ketone *rac*-**2** (1.14 g, 5.45 mmol) in $CHC1_3$ (10 mL) was cooled to −78 °C and stirred under an atmosphere of argon while a solution of PhSeCl (1.04 g, 5.45 mmol) in $CHC1_3$ (10 mL) was added dropwise over 15 min. The reaction mixture was stirred for an additional 30 min at 0 °C and then overnight at rt. The resulting orange solution was diluted with $CHC1_3$ (100 mL) and successively washed with 5% aq Na_2CO_3 (20 mL), H_2O (20 mL), and brine

(30 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated to give 2.10 g of a light orange oil. Crystallization at −20 °C from a mixture of Et_2O/petroleum ether afforded *rac*-**15** (1.57 g, 75%) as a white solid. Elem. Anal. Calcd for $C_{17}H_{20}NO_3ClSe$ (401.03): C, 50.95; H, 5.03; Cl, 8.85; N, 3.5; found C, 50.91; H, 5.01; Cl,8.94; N, 3.44. EI-HRMS (*m*/*z*) calcd for $C_{17}H_{20}NO_3ClSe$ 401.0296, found 401.0300. ^{1}H NMR (300 MHz, $CDCl_3$, 318 K): δ 7.59–7.56 (m, 2H, H-arom), 7.29–7.24 (m, 3H, H-arom), 4.53 (d, 1H, $J_{4,3exo}$=5.51, H-4), 4.35 (d, 1H, $J_{1,6}$=5, H-1), 4.24 (dd, 1H, $J_{6,1}$=5, $J_{6,5}$=3.2, H-6), 3.37 (d, 1H, $J_{5,6}$=3.2, H-5), 2.57 (dd, 1H, $J_{3endo,3exo}$=17.9, $J_{3exo,4}$=5.6, H-3*exo*), 2.11 (d, 1H, $J_{3exo,3endo}$=17.9, H-3*endo*), 1.40 (s, 9H, (CH_3)$_3$C). ^{13}C NMR (75.4 MHz, $CDCl_3$, 318 K): δ 202.3 (CO), 153.6 (*C*OC(CH_3))$_3$, 134.9, 129.5, 128.6, 128.0 (5C, C-arom), 82.1 (*C*(CH_3)$_3$), 67.9 (C-4), 61.7 (C-1), 57.6 (C-6), 44.5 (C-3), 28.1 (*C*H_3)$_3$.

*4.1.8. (±)-7-(tert-Butoxycarbonyl)-2-chloro-7-azabicyclo[2.2.1]hept-5-en-6-one (rac-**16**).* To a solution of *rac*-15 (0.04 g, 0.1 mmol) in CH_2C1_2 (2 mL), stirred at −78 °C under an atmosphere of argon, a solution of *m*-CPBA (0.025 g, 0.1 mmol) in CH_2C1_2 (2 mL) was added dropwise over 30 min. The solution was stirred at −78 °C for 2 h before being warmed to 20 °C, and then was stirred for additional 10 h. Subsequently, the mixture was diluted with CH_2Cl_2 (15 mL) and washed with 5% aq Na_2CO_3 (4 mL), H_2O (4 mL) and brine (4 mL). The organic extract was dried ($MgSO_4$), filtered, and concentrated to give an orange oil that was subjected to column chromatography (EtOAc/petroleum ether, 2:3 v/v), to afford *rac*-**16** (0.021 g, 90%), as a colorless oil. CIMS *m*/*z* 244 [2%, $(M+H)^+$]. EI-HRMS (*m*/*z*) calcd for $C_{11}H_{15}NO_3Cl$ 244.0740, found 244.0729. ^{1}H NMR (400 MHz, $CDCl_3$, 320 K): δ 6.48 (d, *J*=2.3, H-3), 5.05 (m, 1H, H-4), 4.39 (m, 1H, H-1), 2.32 (dd, 1H, *J*=16.1, 3.8, H-5*exo*), 2.01 (d, 1H, *J*=16.1, H-5*endo*), 1.46 (s, 9H, (CH_3)$_3$C). ^{13}C NMR (100.6 MHz, $CDCl_3$, 320 K): δ 202.3 (C-6), 154.7 (*C*O of Boc), 135.9 (C-3), 135.8 (C-2), 82.0 ((CH_3)$_3$*C*), 72.2 (C-1), 61.1 (C-4), 35.3 (C-5), 28.1 ((CH_3)$_3$C).

*4.1.9. (1R,4S)-6-endo-[(1S,4R)-Camphanoyloxy]-2-chloro-7-(tert-butoxycarbonyl)-7-azabicyclo[2.2.1]hept-5-ene (**17**) and (1S,4R)-6-endo-[(1S,4R)-camphanoyloxy]-2-chloro-7-(tert-butoxycarbonyl)-7-azabicyclo[2.2.1]hept-5-ene (**18**).* To a cold (0 °C) solution of *rac*-**7** (0.1 g, 0.407 mmol) in anhydrous CH_2Cl_2 (3 mL) were added Py (1 mL) and (1*S*,4*R*)-(−)-camphanic acid chloride (0.182 g, 0.84 mmol). After stirring for 3 h at rt, a satd aq solution of citric acid was added. The resulting mixture was extracted with CH_2Cl_2, dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography on silica gel (light petroleum ether/AcOEt, 9:1→3:2 v/v) eluting first **17** (0.042 g, 42%) and second **18** (0.044 g, 43%), both as light yellowish solids. Data for **17**: Mp=149–151 °C (AcOEt/hexane); $[\alpha]_D^{25}$ −88.9 (*c* 0.14, $CHCl_3$). CIMS (NH_3): 443 (40, $[M+NH_4]^+$), 426 (18, $[M+H]^+$). ESI-HRMS (*m*/*z*) calcd for $C_{21}H_{29}ClNO_6$+H 426.1683, found 426.1685. IR (film): 2974, 1791, 1736, 1714, 1586, 1369, 1314, 1264, 1165, 1102, 1065, 932, 756 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 320 K): δ 6.36 (br d, 1H, *J*=2.4, H-3), 5.34 (ddd, 1H, *J*=7.8, 4.2, 2.4, H-6), 4.87 (br d, 1H, *J*=4.0, H-1), 4.72–4.69 (m, 1H, H-4), 2.52 (ddd, 1H, *J*=12.3, *J*=8.3, *J*=4.2, H-5*exo*), 2.43–2.36 (m, 1H, camph.), 2.05–1.98 (*m*, 1H, camph.), 1.93–1.86 (m, 1H, camph.), 1.70–1.64 (m, 1H, camph.), 1.44 (*s*, 9H, (CH_3)$_3$C), 1.32 (dd, 1H, *J*=12.6, 2.4, H-5*endo*), 1.11, 1.07, 0.97 (3*s*, 9H, 3 CH_3 of camph.). ^{13}C NMR (100.6 MHz, $CDCl_3$, 320 K): δ 177.8, 167.3 (*C*O of camph.), 154.5 (*C*O of Boc), 135.3 (C-2), 132.1 (C-3), 90.7 (C-1 of camph.), 81.3 ((CH_3)$_3$*C*), 71.9 (C-6), 65.9 (C-1), 61.4 (C-4), 54.8, 54.1 (C-7 and C-4 of camph.), 33.9 (C-5), 30.9 (C-6 of camph.), 29.0 (C-5 of camph.), 28.0 ((CH_3)$_3$C), 16.71, 16.67 (*C*H_3 of camph.), 9.6 (*C*H_3 of camph.). Data for **18**: Mp=178–179 °C (AcOEt/light petroleum ether); $[\alpha]_D^{25}$ +47.0 (*c* 0.3, $CHCl_3$). CIMS (NH_3): 443 (67, $[M+NH_4]^+$). ESI-HRMS (*m*/*z*) calcd for $C_{21}H_{29}ClNO_6$+H 426.1683, found 426.1685. IR (film): 2964, 1788, 1751, 1708, 1586, 1452, 1370, 1347, 1309, 1262, 1172, 1100, 1054, 935 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 320 K): δ 6.38 (br d, 1H, *J*=2.4, H-3), 5.44 (ddd, 1H, *J*=7.8, 4.2, 2.4, H-6), 4.82 (br d, 1H, *J*=4.2, H-1), 4.73–4.70 (m, 1H, H-4), 2.55 (ddd, 1H, *J*=12.3, 7.8, 4.2, H-5*exo*), 2.44–2.36 (m, 1H, camph.), 2.06–1.99 (m, 1H, camph.), 1.93–1.86 (m, 1H, camph.), 1.71–1.64 (m, 1H, camph.), 1.42 (s, 9H, (CH_3)$_3$C), 1.26 (dd, 1H, *J*=12.5, 2.4, H-5*endo*), 1.11, 1.03, 0.97 (3s, 9H, 3 CH_3 of camph.). ^{13}C NMR (100.6 MHz, $CDCl_3$, 320 K): δ 177.6, 167.0 (*C*O of camph.), 154.5 (*C*O of Boc), 135.7 (C-2), 132.1 (C-3), 90.8 (C-1 of camph.), 81.4 ((CH_3)$_3$*C*), 71.6 (C-6), 66.0 (C-1), 61.7 (C-4), 54.9, 54.0 (C-7 and C-4 of camph.), 34.3 (C-5), 30.8 (C-6 of camph.), 29.1 (C-5 of camph.), 28.1 ((CH_3)$_3$C), 16.9, 16.8 (2 CH_3 of camph.), 9.6 (CH_3 of camph.).

*4.1.10. (+)-(1S,4R)-7-(tert-Butoxycarbonyl)-2-chloro-7-azabicyclo[2.2.1]hept-5-en-6-endo-ol ((+)-**7**).* To a solution of **18** (0.25 g, 0.59 mmol) in anhydrous MeOH/THF (10 mL, 6:1 v/v), a catalytic amount of MeONa/MeOH (1 M) was added (pH=8). The solution was stirred for 2 h (TLC monitoring) under pH=8. Then, IR-120(H^+) resin was added until neutral pH was reached, the solution was filtered, and the filtrate was concentrated. The resulting residue was purified by column chromatography (light petroleum ether/AcOEt, 4:1 v/v) to afford (+)-**7** (0.172 g, 99%) as a white solid. Mp=125–127 °C ($CHCl_3$). $[\alpha]_D^{25}$ +72.5 (*c* 0.24, $CHCl_3$).

*4.1.11. (−)-(1R,4S)-7-(tert-Butoxycarbonyl)-2-chloro-7-azabicyclo[2.2.1]hept-5-en-6-endo-ol ((−)-**7**).* This compound was obtained in the manner described for (+)-**7** except that compound **17** was used as starting material. Yield 98%. Mp= 125–127 °C ($CHCl_3$); $[\alpha]_D^{25}$ −74.6 (*c* 0.24, $CHCl_3$).

*4.1.12. (−)-(1R,4S)-7-(tert-Butoxycarbonyl)-2-chloro-7-azabicyclo[2.2.1]hept-5-en-6-one ((−)-**16**).* To a stirred solution of oxalyl chloride (10 μL, 0.12 mmol) in anhydrous CH_2Cl_2 (0.5 mL) at −70 °C, a solution of DMSO (17 μL, 0.24 mmol) in anhydrous CH_2Cl_2 (0.2 mL) was added dropwise. After addition, the mixture was stirred at −70 °C for 15 min and then a solution of alcohol (−)-**7** (25 mg, 0.101 mmol) in anhydrous CH_2Cl_2 (0.4 mL) was added. The mixture was allowed to reach 20 °C, diluted with CH_2Cl_2 (10 mL) and then washed with H_2O. The organic layer was separated and the aqueous phase re-extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on silica gel (light petroleum ether→AcOEt/light petroleum ether (5–20% AcOEt)) to give (−)-**16** (0.02 g, 81%). $[\alpha]_D^{25}$ −377.6 (*c* 0.125, $CHCl_3$).

*4.1.13. (+)-(1S,4R)-7-(tert-Butoxycarbonyl)-2-chloro-7-azabicyclo[2.2.1]hept-5-en-6-one ((+)-**16**).* This compound was prepared in the manner described for (−)-**16** except that alcohol (+)-**7** was used as starting material. Yield 72%. $[\alpha]_D^{25}$ +372.1 (*c* 0.125, $CHCl_3$).

*4.1.14. (−)-(2S,3R,5R)-N-(tert-Butoxycarbonyl)-5-dimethoxymethyl-3-hydroxy-2-methoxycarbonylpyrrolidine ((−)-**19**).* This compound was prepared in the manner described for **14** except that alcohol (+)-**7** was used as starting material. Yield 62%. White solid. $[\alpha]_D^{25}$ −15 (*c* 0.91, CH_2Cl_2). FAB-HRMS (*m*/*z*) calcd for $C_{14}H_{25}NO_7Na$. 342.1528, found: 342.1517. IR (film): 3411, 2975, 1764, 1698, 1454, 1392, 1175, 1122, 1093, 1055, 1014, 915 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 4.74 (d, 1H, *J*=1.9, C*H*(OMe)$_2$), 4.43 (m, 1H, H-3), 4.32 (d, 1H, *J*=5.5, H-5), 4.08 (m, 1H, H-2), 3.74 (s, 3H, OCH_3), 3.68 (*s*, 3H, OCH_3), 3.48 (*s*, 3H, OCH_3), 2.20–2.16 (*m*, 2H, H-4a, H-4b), 1.40 (*s*, 9H, (CH_3)$_3$C). ^{13}C NMR (100.6 MHz, $CDCl_3$, 298 K): δ 169.3 (*C*OOMe), 154.5 (*C*O of Boc), 104.8 (*C*H(OMe)$_2$), 80.7 (*C*(CH_3)$_3$), 71.6 (C-3), 60.7 (C-5), 59.8 (OCH_3), 57.8 (C-2), 56.5 (OCH_3), 51.7 (OCH_3), 32.9 (C-4), 27.9 ((CH_3)$_3$C).

*4.1.15. (+)-(2R,3S,5S)-N-(tert-Butoxycarbonyl)-5-dimethoxymethyl-3-hydroxy-2-methoxycarbonylpyrrolidine ((+)-**19**).* This compound was obtained in the manner described for **14** except that compound

(−)-**7** was used as starting material. Yield 60%. $[\alpha]_D^{25}$ +17 (*c* 0.91, CH_2Cl_2).

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Supplementary data

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References and notes

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