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Selective Synthesis of New Fluorinated Alicyclic β-Amino Ester Stereoisomers

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New fluorinated alicyclic β-amino ester stereoisomers with a cyclohexene or cyclohexane skeleton were prepared from *cis*- or *trans*-2-aminocyclohex-3-enecarboxylic acids in five or six steps through a regio- and stereoselective hydroxylation and hydroxy–fluorine exchange. Fluorinated amino ester enantiomers were synthesized from enantiopure *cis*- or *trans*-2-aminocyclohexenecarboxylic acid (prepared by enzymatic resolution of the racemic substances).

Introduction

Conformationally rigid cyclic β-amino acids are considered of high importance for synthetic and medicinal chemistry, and particularly for the synthesis of new bioactive molecules. These compounds are key elements in natural products and precursors to bioactive β-lactams. A number of β-amino acids, such as cispentacin, oxetin, oryzoxymicin, and icofungipen, are important antifungal or antibacterial agents. The alicyclic or heterocyclic conformationally restricted β-amino acids are building blocks in the synthesis of new biologically active peptides.[1]

As a consequence of fluorine being present in many important pharmacological compounds, organic chemistry involving fluorinated drugs and agrochemicals has undergone enormous developments in the past 20 years. However, although fluorine is not present in biologically active natural compounds, an increasing number of drugs on the market contain at least one fluorine atom. It is noteworthy that the replacement of one or more atoms or functional groups by fluorine in biologically active molecules can lead to profound changes in their physical, chemical, and especially biological properties.[2]

Accordingly, an increasing number of fluorinated derivatives of natural products and other bioactive compounds have been prepared. Fluorinated amino acids[3] and peptides[4] are recognized as valuable biomolecules in medicinal chemistry and biochemistry, as antibiotics, enzyme inhibitors, or antitumor agents.

Although the cyclic amino acids exhibit high pharmaceutical potential, relatively few cyclic fluorinated derivatives have been reported, among either α-amino acids[3a,5] or γ-amino acids.[3a,6] Despite their importance in pharmaceutical and peptide chemistry and the fact that cyclic β-amino acids have undergone intensive research in recent years,[1] only a small number of fluorinated derivatives have been synthesized so far.[3f,7,8]

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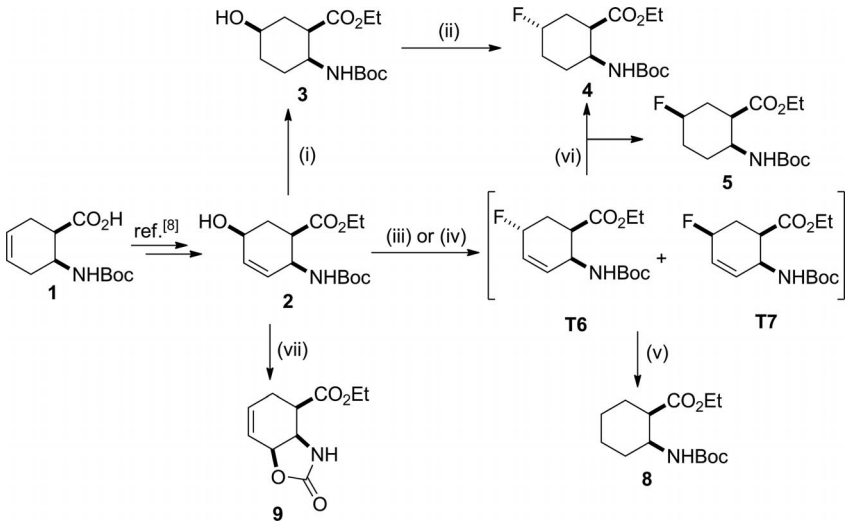
Results and Discussion

Herein, we report on the regio- and stereoselective syntheses of new mono- and difluorinated cyclohexane β-amino acids. The stereo- and regioselective introduction of a fluorine atom to the cyclohexane skeleton was accomplished by a hydroxy–fluorine exchange approach. As in our earlier experiments, the racemic *N*-Boc-protected (*tert*-butoxycarbonyl) starting materials *cis*- and *trans*-2-aminocyclohex-3-enecarboxylic acid (**1** and **16**, respectively) were first regio- and stereoselectively hydroxylated by iodolactonization and lactone-opening procedures, as key steps resulting in the hydroxylated amino ester stereoisomers **2**, **10**, and **17**.[9] The C–C double bond of all-*cis*-hydroxylated cyclohexene β-amino ester **2** derived from amino acid **1** (Scheme 1) was saturated first to give ethyl 5-hydroxy-2-aminocyclohexanecarboxylate **3**. Amino ester **3** was then subjected to hydroxy–fluorine exchange by using different fluorinated organic reagents. Fluorination with bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor) in CH_2Cl_2 at 20 °C for 15 h resulted in the inversion of configuration to give the 5-fluorinated amino ester **4** (Scheme 1), which was easily separated from the small amount of elimination side products by chromatography. A similar result was obtained using diethylaminosulfur trifluoride (DAST). An interesting and somewhat surprising experimental result was observed when *cis*-hydroxylated cyclohexene β-amino ester **2** was subjected to fluorination. Upon treatment with either Deoxo-Fluor or DAST, amino ester **2**, with a C–C double bond in the ring, furnished a mixture of two fluorinated products in approximately a 1:1 ratio (the ratio of the mixture of **T6** and **T7** was determined by analysis of the



Scheme 1. Synthesis of fluorinated β-amino acids **4** and **5** by fluorination of all-*cis*-hydroxylated amino ester **2**. Reagents and conditions: (i) $HCOONH_4$, 10% Pd/C, EtOH, 70 °C, 1 h, 87%; (ii) Deoxo-Fluor, CH_2Cl_2, 20 °C, 15 h, 40%; (iii) 1.5 equiv. Deoxo-Fluor, CH_2Cl_2, 20 °C, 13 h, 63%, (**T6/T7**, 1:1); (iv) 1.3 equiv. DAST, CH_2Cl_2, 20 °C, 13 h, 55%, (**T6/T7**, 1:1); (v) H_2, 10% Pd/C, EtOH, 20 °C, 1 h, 82%; (vi) H_2, 10% Pd/C, EtOAc, 20 °C, 1 h, **4** (22% from **2**), **5** (22% from **2**); (vii) FLUOLEAD, CH_2Cl_2, 20 °C, 15 h, 78%.

NMR spectroscopic data for the crude mixture), which could not be separated by either crystallization or chromatography. To separate and characterize the two fluorinated amino esters, hydrogenation of the ring double bond was effected. Hydrogenation in the presence of 10% Pd/C in EtOH, resulted in saturation and removal of the fluorine to give amino ester **8** (Scheme 1). When the mixture of **T6** and **T7** was hydrogenated in the presence of the Pd/C catalyst in EtOAc, the corresponding saturated derivatives could be separated by chromatography, affording β-amino esters **4** and **5**, each consisting of the 5-fluorocyclohexane skeleton (Scheme 1). This experimental result indicated that, in contrast to fluorination occurring by an S_N2 process leading to inversion at the hydroxyl site of cyclohexane amino ester **3**, fluorination of hydroxylated cyclohexene amino ester **2** proceeded by an S_N1 mechanism. Compounds **4** and **5** were synthesized earlier under similar conditions from all-*cis*-ethyl-2-(*tert*-butoxycarbonylamino)-3-hydroxycyclohex-4-enecarboxylate.[8]

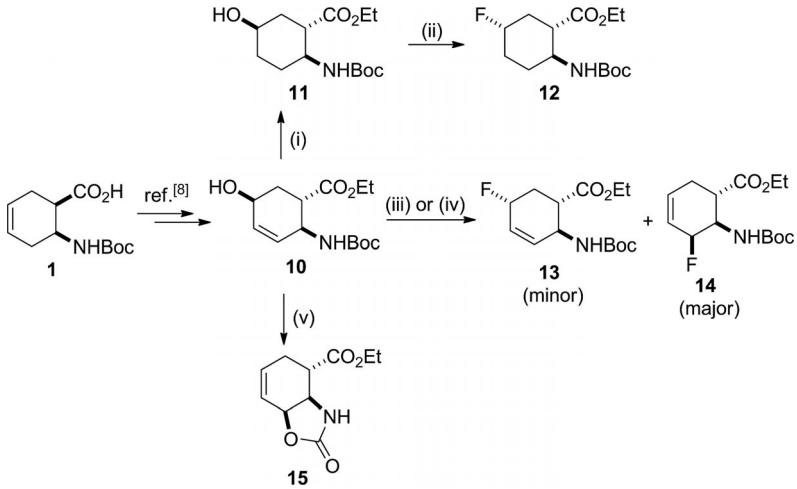
Although the synthesis of the fluorinated cyclohexane amino esters could be achieved, preparation of their unsaturated counterparts remained unresolved. Since the fluorination of **2** with either Deoxo-Fluor or DAST furnished an inseparable mixture, we attempted the reaction with a new fluorinating agent, 2,4,6-trimethylbenzenesulfur trifluoride (FLUOLEAD). Unfortunately no fluorinated product resulted, but oxazolinone derivative **9** was obtained in good yield, involving an intramolecular nucleophilic attack of the carbamate's oxygen atom on C-3 by an S_N2' process (Scheme 1).

Next, the fluorination of amino ester **10**, the C-1 epimer of **2** which is derived from *cis*-amino acid **1**, was investigated. Saturation of the C–C double bond in **10** gave **11**, which then yielded 5-fluoro β-aminocarboxylate **12** (Scheme 2). This desired fluorinated derivative was easily separated from a relatively small quantity of elimination side products by chromatography.

The fluorination of amino ester **10** gave the expected inversion product **13** (an S_N2 product, see Figure 1) as the minor product and 3-fluorinated derivative **14** as the major product, identified by 2D NMR analysis. To determine of the stereochemistry of **14**, a chemical correlation approach was applied. Ethyl (1*S**,2*R**,3*R**)-2-(*tert*-butoxycarbonylamino)-3-fluorocyclohexanecarboxylate, where the amino moiety and fluorine atom are *trans* to each other, was prepared earlier by our group.[8] Hydrogenation of **14** produced ethyl (1*S**,2*R**,3*S**)-2-(*tert*-butoxycarbonylamino)-3-fluorocyclohexanecarboxylate, where the amino group and fluorine atom are *cis* to each other, a diastereomer of the previously synthesized ethyl (1*S**,2*R**,3*R**)-2-(*tert*-butoxycarbonylamino)-3-fluorocyclohexanecarboxylate.

A possible mechanistic route to **13** and **14** is proposed in Figure 2. Treatment of hydroxylated amino ester **10** with DAST probably involves synchronized processes. A new oxygen–sulfur bond is formed while simultaneously breaking a sulfur–fluorine bond (**S1**), which is then followed by an intramolecular attack of the fluoride anion on the sp^2 carbon atom (**S2**) to afford **14** as the major product (Figure 2, path a). Although less favorable, an alternate competitive process involving an intramolecular equatorial fluoride attack results in inversion to give the substitution product **13** as the minor isomer.

Compounds **13** and **14** were readily separated by flash chromatography (Scheme 2). In view of our earlier results, formation of **14** by an S_N2' mechanism was predictable (Figure 3), and the fluorination of unsaturated cyclic hydroxylated amino esters furnished such products.[8] Oxazolinone derivative **15** was obtained as the sole product in



Scheme 2. Synthesis of fluorinated β-amino acids **12**, **13**, and **14** from hydroxylated amino ester **10**. Reagents and conditions: (i) $HCOONH_4$, 10% Pd/C, EtOH, 70 °C, 1 h, 84%; (ii) Deoxo-Fluor (1.5 equiv.), CH_2Cl_2, 20 °C, 15 h, 53%; (iii) Deoxo-Fluor (1.5 equiv.), CH_2Cl_2, 20 °C, 13 h, **13** (27%), **14** (41%); (iv) DAST (1.3 equiv.), CH_2Cl_2, 20 °C, 13 h, **13** (31%), **14** (42%); (v) FLUOLEAD, CH_2Cl_2, 20 °C, 15 h, 69%.

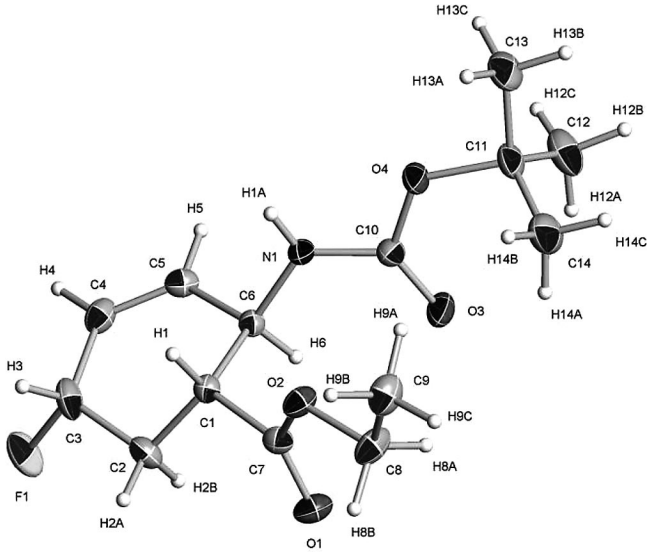


Figure 1. ORTEP diagram of **13**.

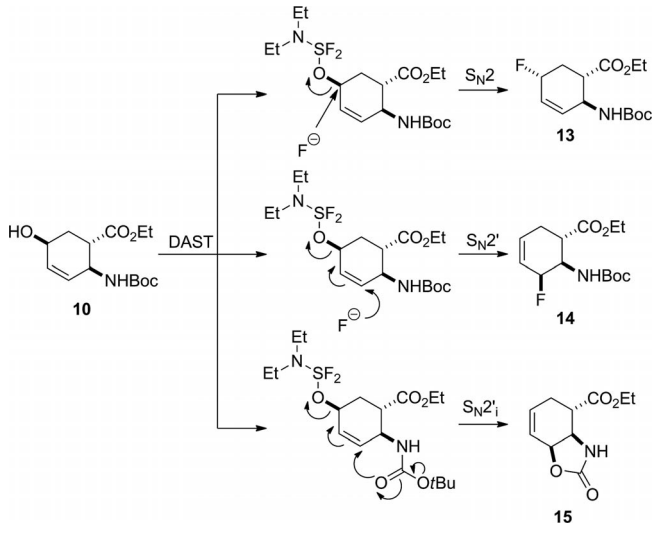


Figure 3. Formation of fluorinated amino esters **13** and **14** and oxazolinone derivative **15**.

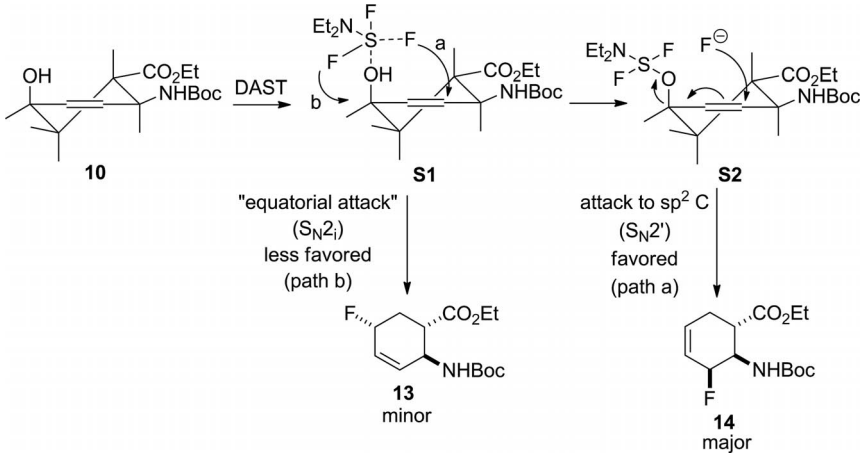
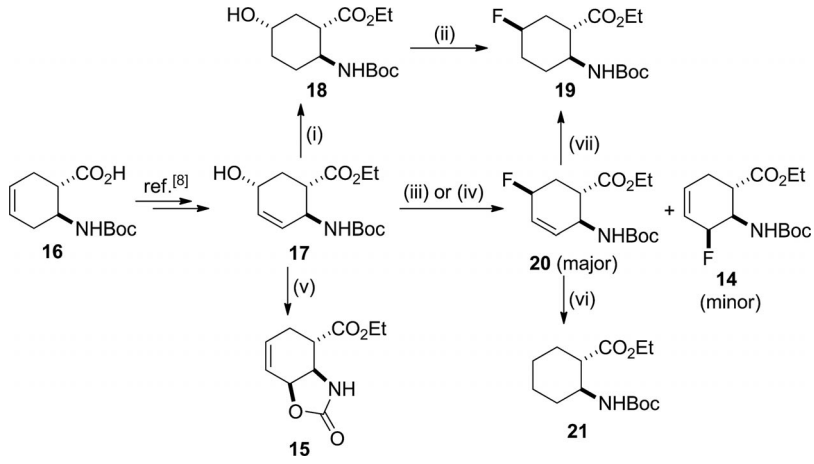


Figure 2. Proposed routes for the formation of **13** and **14**.



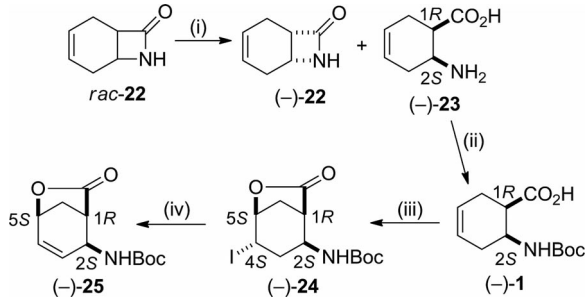
Scheme 3. Synthesis of fluorinated amino esters **19**, **14**, and **20**. Reagents and conditions: (i) $HCOONH_4$, 10% Pd/C, EtOH, 70 °C, 1 h, 86%; (ii) 1. Deoxo-Fluor (5 equiv.), CH_2Cl_2, 20 °C, 15 h, 60%; (iii) Deoxo-Fluor (4.0 equiv.), CH_2Cl_2, 20 °C, 13 h, **20** (58%), **14** (5%); (iv) DAST (1.3 equiv.), CH_2Cl_2, 20 °C, 13 h, **20** (57%), **14** (5%); (v) FLUOLEAD, CH_2Cl_2, 20 °C, 15 h, 66%. (vi) H_2, 10% Pd/C, EtOH, 20 °C, 1 h, 78%; (vii) H_2, 10% Pd/C, EtOAc, 20 °C, 1 h, 82%.

moderate yield from **10** upon treatment with FLUOLEAD (Scheme 2, Figure 3). To prepare other new fluorinated 2-aminocarboxylate stereoisomers, hydroxylated β-amino ester stereoisomer **17** (derived from *trans*-β-amino acid **16**) was first reduced to give **18**. Fluorination of **18** with Deoxo-Fluor afforded the corresponding 5-fluoro-amino ester **19** in 60% yield (Scheme 3).

Direct fluorination of **17** by treatment with Deoxo-Fluor or DAST resulted, analogously as in the case of its stereoisomer **10**, in both 5- and 3-fluorinated derivatives **20** (S_N2 product) and **14** (S_N2' product), respectively. However, somewhat surprising and in contrast with the fluorination of **10**, the major product in this transformation was the 5-fluorinated derivative **20** (Scheme 3).

The difference in the reactivity between **10** and **17** and the product ratio (**14/20**) may be explained by considering the processes illustrated in Figure 4. Again, a synchronized process is probably responsible for the ratio of the fluorinated products. In intermediate **S3**, the two competing processes are an intramolecular fluoride attack on the sp^2 C atom (path b, leading to **14** as the minor isomer) and an intramolecular substitution with inversion by an "axial attack" (path a, affording **20** as the major product).

Compound **20** was synthesized earlier by an alternate route, as an S_N2' product from ethyl (1*S**,2*R**,3*S**)-6-(*tert*-butoxycarbonylamino)-3-hydroxycyclohex-4-enecarboxylate.[8] The formation of **20** was also confirmed by hydrogen-



Scheme 4. Enzymatic resolution of racemic azetidinone **22**. Reagents and conditions: (i) CAL-B (Lipase B from Candida antarctica), H_2O (0.5 equiv.), iPr_2O, 60 °C; (ii) Boc_2O, 10% NaOH, H_2O/THF, 0 °C to 20 °C, 12 h, 76%. (iii) KI, I_2, $NaHCO_3$, H_2O/CH_2Cl_2, 20 °C, 16 h, 79%; (iv) DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene), THF (tetrahydrofuran), 65 °C, 4 h, 69%.

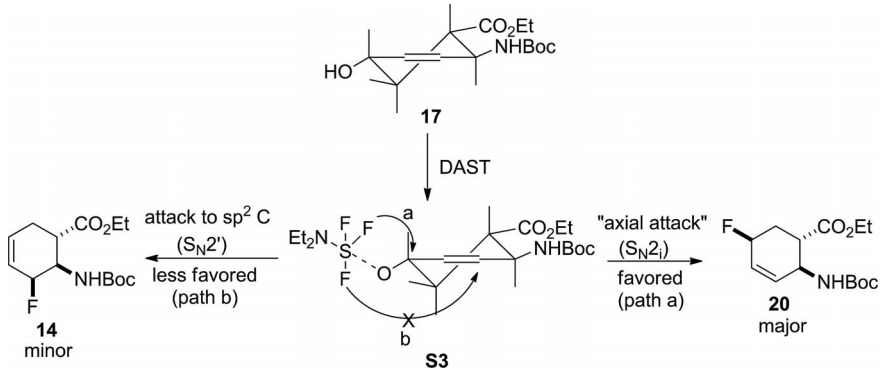
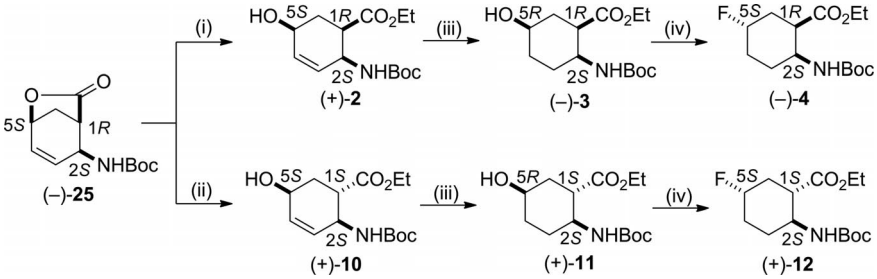


Figure 4. Proposed routes for the formation of **14** and **20**.



Scheme 5. Synthesis of enantiomerically pure fluorinated amino esters (–)-**4** and (+)-**12**. Reagents and conditions: (i) NaOEt, EtOH, 0 °C, 1 h, 70%; (ii) NaOEt, EtOH, 20 °C, 10 h, 66%. (iii) $HCOONH_4$, Pd/C, EtOH, 70 °C, 1 h, (–)-**3** (83%), (+)-**11** (81%); (iv) DAST, CH_2Cl_2, 20 °C, 7 h, (–)-**4** (43%), (+)-**12** (45%).

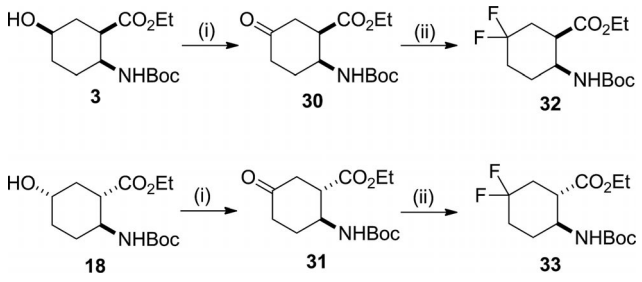
ation in EtOAc which led to saturated product **19**, whereas hydrogenation in EtOH was accompanied by removal of the fluorine to give amino ester **21** (Scheme 3).

The synthetic route presented offered a possibility for the preparation of enantiomeric substances. Enantiomerically pure β-amino acid (–)-**23** (> 98%*ee*)[10] was prepared by the Lipolase-catalyzed (Lipase B from Candida antarctica) enantioselective ring cleavage of unsaturated racemic β-lactam **22**.[11] High enantioselectivity (E > 200) was observed when the reaction was performed with 0.5 equiv. of H_2O in iPr_2O at 60 °C. Enantiopure (–)-**23** was further transformed under the earlier experimental conditions to lactone (–)-**25** (Scheme 4), from which the hydroxylated amino esters (+)-**2** and (+)-**10** were prepared in optically pure form.

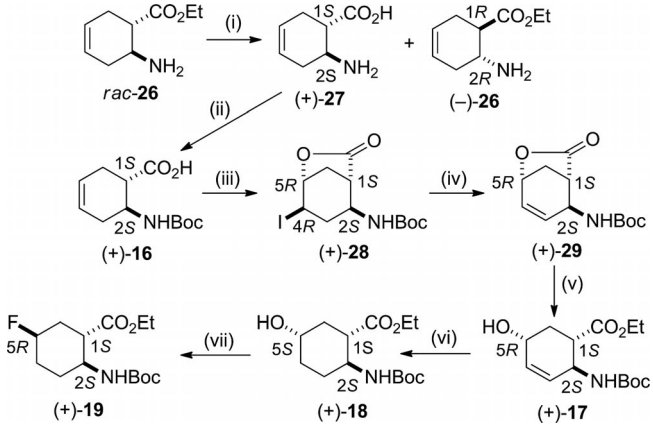
Hydrogenation of (+)-**2** and (+)-**10** to (–)-**3** and (+)-**11**, respectively, followed by fluorination furnished the corresponding fluorinated aminocyclohexanecarboxylate enantiomers (–)-**4** and (+)-**12** (98%*ee*, Scheme 5). Enantiomer (–)-**4** was prepared earlier through an alternate route.[8]

Enantiopure (> 98%*ee*) *trans*-β-amino acid (+)-**27**[10] was obtained through the Lipolase-catalyzed enantioselective (E > 100) hydrolysis (0.5 equiv. of H_2O) of racemic *trans*-β-amino ester **26**, in iPr_2O at 60 °C.[12] By following a similar reaction pathway as that for the racemic substance, transformation of the enantiopure *trans*-β-amino acid (+)-**27** afforded fluorinated amino ester enantiomer (+)-**19** (94%*ee*, Scheme 6).

New geminal difluorinated cyclohexane β-amino esters were synthesized by selective hydroxylation through the corresponding keto-aminocarboxylates. Hydroxylated amino esters **3** and **18** were converted with a sulfur trioxide–pyr-



Scheme 7. Synthesis of difluorinated amino esters **32** and **33**. Reagents and conditions: (i) Py–SO_3, DMSO, Et_3N CH_2Cl_2, 20 °C, 20 h, **30**: 76%, **31**: 73%. (ii) Deoxo-Fluor, CH_2Cl_2, 1 drop of EtOH, 0 °C, 8 h, **32** (36%), **33** (37%).



Scheme 6. Synthesis of enantiomerically pure fluorinated amino ester (+)-**19**. Reagents and conditions: (i) Lipase PS, H_2O, Et_2O. (ii) Boc_2O, 10% NaOH, H_2O/THF, 0 °C to 20 °C, 12 h, 79%. (iii) I_2, KI, $NaHCO_3$, H_2O, CH_2Cl_2, 20 °C, 14 h, 86%. (iv) DBU, THF, 65 °C, 4 h, 69%. (v) NaOEt, EtOH, 20 °C, 7 h, 68%; (vi) $HCOONH_4$, Pd/C, EtOH, 70 °C, 1 h, 79%. (vii) DAST, CH_2Cl_2, 20 °C, 6 h, 41%.

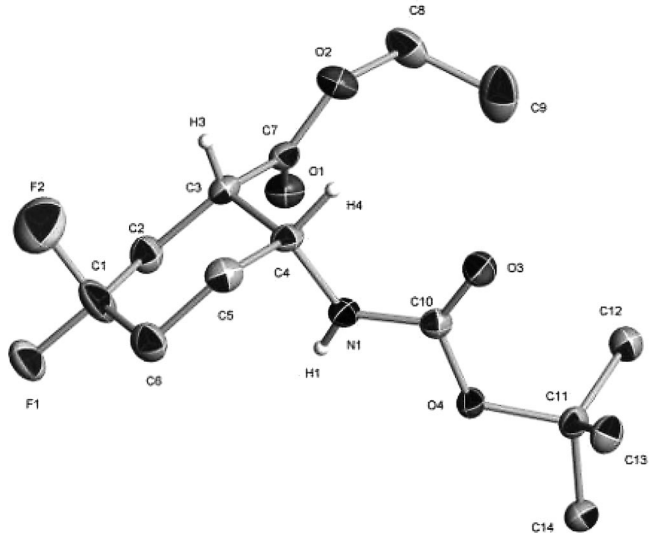


Figure 5. ORTEP diagram of **32**.

idine complex in the presence of Et_3N and DMSO (dimethyl sulfoxide) to the corresponding 5-keto-2-amino esters **30** and **31**, respectively. (Scheme 7). Upon treatment with Deoxo-Fluor and one drop of EtOH in CH_2Cl_2, the oxocarboxylates led to difluorinated amino esters **32** and **33** (Scheme 7, Figure 5).

Conclusions

A simple diastereo- and regioselective method has been applied for the synthesis of new mono- or difluorinated cyclohexane or cyclohexene β-amino esters through selective hydroxylation and hydroxy–fluorine exchange. The synthetic procedure was also extended to the preparation of these derivatives in enantiomerically pure form.

Experimental Section

General Procedure for Reduction of 2, 10, and 17: To a solution of hydroxy amino ester **2**, **10**, or **17** (1.65 mmol) in EtOH (20 mL) was added $HCOONH_4$ (8.25 mmol, 5 equiv.) and Pd/C (10%, 90 mg). The mixture was stirred at 75 °C. After 1 h, the solids were filtered, and the filtrate was concentrated and purified by chromatography on silica gel (*n*-hexane/EtOAc, 1:1).

General Procedure for Reduction of T6, T7, and 20: To a solution of a mixture of fluorinated amino esters **T6**, **T7**, and **20** (1.5 mmol) in EtOAc (15 mL) was added Pd/C (10%, 70 mg) The mixture was stirred under a H_2 atmosphere for 2 h, and the solids were then filtered through Celite. The filtrate was concentrated, and the crude product was separated and purified by column chromatography on silica gel (*n*-hexane/EtOAc, 9:1).

Ethyl (1*R,2*S**,5*R**)-2-(*tert*-Butoxycarbonylamino)-5-hydroxycyclohexanecarboxylate (3):** A colorless oil (87%). R_f = 0.45 (*n*-hexane/EtOAc, 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, J = 7.10 Hz, 3 H, CH_3), 1.43 (s, 9 H, *t*Bu), 1.52–1.79 (m, 3 H, CH_2), 1.89–2.10 (m, 3 H, CH_2), 2.76–2.82 (m, 1 H, 1-H), 3.80–3.85 (m, 1 H, 2-H), 3.90–3.99 (m, 1 H, 5-H), 4.11–4.20 (m, 2 H, OCH_2), 5.20 (br. s, 1 H, NH) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.6, 26.4, 28.7, 31.4, 33.5, 43.2, 48.3, 61.1, 67.1, 79.7, 155.6, 174.5 ppm. $C_{14}H_{25}NO_5$ (287.36): calcd. C 58.52, H 8.77, N 4.87; found C 58.19, H 8.55, N 4.48.

Ethyl (1*S,2*S**,5*R**)-2-(*tert*-Butoxycarbonylamino)-5-hydroxycyclohexanecarboxylate (11):** A colorless oil (84%). R_f = 0.4 (*n*-hexane/EtOAc, 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.10 Hz, 3 H, CH_3), 1.42 (s, 9 H, *t*Bu), 1.57–2.00 (m, 6 H, CH_2), 2.68–2.79 (m, 1 H, 1-H), 3.68–3.80 (m, 1 H, 2-H), 4.07–4.20 (m, 3 H, OCH_2 and 5-H), 4.61 (br. s, 1 H, NH) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.6, 27.2, 28.7, 31.3, 31.6, 35.1, 44.6, 50.9, 61.0, 65.0, 79.7, 155.4, 174.3 ppm. $C_{14}H_{25}NO_5$ (287.36): calcd. C 58.52, H 8.77, N 4.87; found C 58.22, H 8.42, N 4.50.

Ethyl (1*S,2*S**,5*S**)-2-(*tert*-Butoxycarbonylamino)-5-hydroxycyclohexanecarboxylate (18):** A white solid (86%), m.p. 125–128 °C. R_f = 0.4 (*n*-hexane/EtOAc, 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.10 Hz, 3 H, CH_3), 1.41 (s, 9 H, *t*Bu), 1.36–1.43 (m, 1 H, CH_2), 1.66–1.71 (m, 1 H, CH_2), 1.83–2.21 (m, 4 H, CH_2), 2.36–2.42 (m, 1 H, 1-H), 3.58–3.77 (m, 2 H, 2-H and 5-H), 4.15–4.20 (m, 2 H, OCH_2), 4.51–4.61 (br. s, 1 H, NH) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.5, 28.7, 31.0, 34.0, 37.1, 48.4, 51.2, 61.2, 69.1, 79.8, 155.4, 173.9 ppm. $C_{14}H_{25}NO_5$ (287.36): calcd. C 58.52, H 8.77, N 4.87; found C 58.17, H 8.51, N 4.49.

General Procedure for Fluorination

Method A: To a solution of hydroxy amino ester **2**, **3**, **10**, **11**, **17**, or **18** (0.55 mmol) in CH_2Cl_2 (5 mL) under an Ar atmosphere was added Deoxo-Fluor (50%) in toluene (1.5 equiv.), and the solution was stirred at 20 °C for 13 h. The solution was then diluted with CH_2Cl_2 (20 mL), and the organic layer was washed with a saturated aqueous $NaHCO_3$ solution (2 × 15 mL). The organic layer was dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 9:1).

Method B: To a solution of hydroxy amino ester **2**, **10**, or **17**) (0.55 mmol) in CH_2Cl_2 (5 mL) under an Ar atmosphere was added DAST (1.3 equiv.), and the solution was stirred at 20 °C for 13 h. The solution was then diluted with CH_2Cl_2 (20 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ solution (2 × 15 mL). The organic layer was dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 9:1).

Ethyl (1*R,2*S**,5*S**)-2-(*tert*-Butoxycarbonylamino)-5-fluorocyclohexanecarboxylate (4):** Yield 22%, see ref.[8]

Ethyl (1*R,2*S**,5*R**)-2-(*tert*-Butoxycarbonylamino)-5-fluorocyclohexanecarboxylate (5):** Yield 22%, see ref.[8]

Ethyl (1*S,2*S**,5*S**)-2-(*tert*-Butoxycarbonylamino)-5-fluorocyclohexanecarboxylate (12):** A white solid (53%), m.p. 73–75 °C (*n*-hexane). R_f = 0.7 (*n*-hexane/EtOAc, 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.20 (t, J = 7.15 Hz, 3 H, CH_3), 1.31 (s, 9 H, *t*Bu), 1.49–1.62 (m, 2 H, CH_2), 1.77–1.82 (m, 1 H, CH_2), 1.99–2.15 (m, 2 H, CH_2), 2.20–2.28 (m, 1 H, CH_2), 2.27–2.33 (m, 1 H, 1-H), 3.58–3.67 (m, 1 H, 2-H), 4.10–4.17 (m, 2 H, OCH_2), 4.30–4.57 (m, 2 H, 5-H and NH) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.5, 28.7, 30.0, 31.3, 34.4, 47.6, 50.9, 61.4, 80.0, 89.0, 91.3, 155.3, 172.6 ppm. $C_{14}H_{24}FNO_4$ (289.35): calcd. C 58.11, H 8.36, N 4.84; found C 57.83, H 8.00, N 4.54. HRMS: calcd. for $C_{14}H_{24}FNO_4$ $[M]^+$ 289.1689; found 289.1699.

Ethyl (1*S,2*S**,5*R**)-2-(*tert*-Butoxycarbonylamino)-5-fluorocyclohex-3-enecarboxylate (13):** A white solid (Method A, 27%; Method B, 31%), m.p. 113–115 °C (hexane). R_f = 0.65 (*n*-hexane/EtOAc, 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.15 Hz, 3 H, CH_3), 1.46 (s, 9 H, *t*Bu), 2.01–2.17 (m, 1 H, CH_2), 2.34–2.42 (m, 1 H, CH_2), 2.56–2.68 (m, 1 H, 1-H), 4–18–2.29 (m, 2 H, OCH_2), 4.44–4.53 (m, 1 H, 2-H), 4.60 (br. s, 1 H, NH), 5.10–5.28 (m, 1 H, 5-H), 5.70–5.97 (m, 2 H, 3-H and 4-H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.5, 28.7, 31.8, 32.1, 45.5, 61.5, 85.7, 87.9, 128.7, 133.0, 155.3, 172.6 ppm. $C_{14}H_{22}FNO_4$ (287.33): calcd. C 58.52, H 7.72, N 4.87; found C 58.16, H 7.56, N 4.50. HRMS: calcd. for $C_{14}H_{24}FNO_4$ $[M + Na]^+$ 310.1431; found 310.1423.

Ethyl (1*S,2*R**,3*S**)-2-(*tert*-Butoxycarbonylamino)-3-fluorocyclohex-4-enecarboxylate (14):** A colorless oil (Method A, 41%; Method B, 42%). R_f = 0.68 (*n*-hexane/EtOAc, 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.19 (t, J = 7.15 Hz, 3 H, CH_3), 1.38 (s, 9 H, *t*Bu), 2.30–2.43 (m, 1 H, CH_2), 2.62–2.73 (m, 1 H, 1-H), 4.01–4.16 (m, 3 H, OCH_2 and 2-H), 4.63–4.85 (m, 1 H, 3-H), 4.86 (br. s, 1 H, NH), 5.78–5.83 (m, 1 H, 5-H), 5.92–6.00 (m, 1 H, 4-H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.1, 28.3, 28.5, 41.1, 51.1, 60.9, 82.4, 84.6, 86.0, 122.9, 133.5, 154.9, 172.8 ppm. $C_{14}H_{22}FNO_4$ (287.33): calcd. C 58.52, H 7.72, N 4.87; found C 58.14, H 8.00, N 4.53. HRMS: calcd. for $C_{14}H_{24}FNO_4$ $[M + Na]^+$ 310.1431; found 310.1425.

Ethyl (1*S,2*S**,5*R**)-2-(*tert*-Butoxycarbonylamino)-5-fluorocyclohexanecarboxylate (19):** A white solid (60%), m.p. 81–83 °C (*n*-hexane). R_f = 0.7, (*n*-hexane/EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (t, J = 7.15 Hz, 3 H, CH_3), 1.37 (s, 9 H, *t*Bu), 1.42–2.19 (m, 6 H, CH_2), 2.51–2.62 (m, 1 H, 1-H), 3.61–3.71 (m, 1 H, 2-H), 4.05–4.13 (m, 2 H, OCH_2), 5.50 (br. s, 1 H, NH), 4.65–4.91 (m, 1 H, 5-H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.6, 27.6, 28.7, 29.9, 31.3, 33.3, 44.9, 61.2, 77.7, 86.2, 88.5, 156.0, 173.4 ppm. $C_{14}H_{24}FNO_4$ (289.35): calcd. C 58.11, H 8.36, N 4.84; found C 57.86, H 8.02, N 4.53.

Ethyl (1*S,2*S**,5*S**)-2-(*tert*-Butoxycarbonyl)-5-fluorocyclohex-3-enecarboxylate (20):** Yield 63%, see ref.[8]

Ethyl (3a*R,4*R**,7a*S**)-2-Oxo-2,3,3a,4,5,7a-hexahydrobenzo[*d*]oxazole-4-carboxylate (9):** A white solid (78%), m.p. 98–100 °C (*n*-hexane/EtOAc). R_f = 0.35 (*n*-hexane/EtOAc, 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, J = 7.10 Hz, 3 H, CH_3), 2.39–2.47 (m, 2 H, CH_2), 2.68–2.80 (m, 1 H, 4-H), 4.19–4.28 (m, 2 H, OCH_2), 4.48–4.51 (m, 1 H, 3a-H), 5.08–5.11 (m, 1 H, 7a-H), 5.55 (br. s, 1 H, NH), 5.74–5.78 (m, 1 H, 6-H), 6.09–6.15 (m, 1 H, 7-H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.7, 22.8, 42.1, 52.0, 61.9, 73.4, 123.8, 132.4, 158.7, 173.9 ppm. $C_{10}H_{13}NO_4$ (211.22): calcd. C 56.86, H 6.20, N 6.63; found C 56.60, H 5.86, N 6.41.

Ethyl (3a*R,4*S**,7a*S**)-2-Oxo-2,3,3a,4,5,7a-hexahydrobenzo[*d*]oxazole-4-carboxylate (15):** A white solid [69% (66%)], m.p. 115–118 °C (*n*-hexane/EtOAc). R_f = 0.40 (*n*-hexane/EtOAc, 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (t, J = 7.10 Hz, 3 H, CH_3), 2.08–2.17 (m, 1 H, CH_2), 2.56–2.65 (m, 2 H, 4-H and CH_2), 3.92–4.00 (m, 1 H, 3a-H), 4.20–4.29 (m, 2 H, OCH_2), 4.92–5.03 (m, 1 H, 7a-H), 5.96 (br. s, 1 H, NH), 5.98–6.02 (m, 1 H, 6-H), 6.18–6.21 (m, 1 H, 7-H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.6, 25.5, 43.4, 53.2, 61.8, 72.6, 123.7, 132.3, 158.8, 173.2 ppm. $C_{10}H_{13}NO_4$ (211.22): calcd. C 56.86, H 6.20, N 6.63; found C 56.99, H 6.53, N 6.44. HRMS: calcd. for $C_{10}H_{13}NO_4$ $[M]^+$ 211.0845; found 211.0853.

Ethyl (1*R,2*S**)-2-(*tert*-Butoxycarbonylamino)cyclohexanecarboxylate (8):** A white solid (82%), m.p. 54–57 °C (*n*-hexane). R_f = 0.45 (*n*-hexane/EtOAc, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.15 Hz, 3 H), 1.48 (s, 9 H, *t*Bu), 1.55–2.12 (m, 8 H, CH_2), 2.74–2.78 (m, 1 H, 1-H), 3.77–3.86 (m, 1 H, 2-H), 4.13–4.25 (m, 2 H, OCH_2), 5.28 (br. s, 1 H, NH) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.6, 22.9, 24.1, 27.3, 28.7, 30.2, 45.2, 49.5, 60.7, 79.5, 155.6, 174.3 ppm. $C_{14}H_{25}NO_4$ (271.36): calcd. C 61.97, H 9.29, N 5.16; found C 61.65, H 8.96, N 4.90.

Ethyl (1*S,2*S**)-2-(*tert*-Butoxycarbonylamino)cyclohexanecarboxylate (21):** A white solid (78%), m.p. 65–67 °C (*n*-hexane). R_f = 0.45 (*n*-hexane/EtOAc, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12–1.26 (m, 1 H, CH_2), 1.24 (t, J = 7.15 Hz, 3 H), 1.48 (s, 9 H, *t*Bu), 1.53–2.20 (m, 7 H, CH_2), 2.20–2.26 (m, 1 H, 1-H), 3.62–3.74 (m, 1 H, 2-H), 4.12–4.22 (m, 2 H, OCH_2), 4.51 (br. s, 1 H, NH) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.7, 22.9, 24.6, 27.8, 29.5, 30.9, 45.1, 49.8, 61.0, 79.8, 155.2, 174.7 ppm. $C_{14}H_{25}NO_4$ (271.36): calcd. C 61.97, H 9.29, N 5.16; found C 61.60, H 8.98, N 4.88.

General Procedure for Oxidation of 3 or 18: To a solution of amino ester **3** or **18** (3 mmol) in CH_2Cl_2 (25 mL) was added Et_3N (4.0 equiv.), sulfur trioxide–pyridine complex (3.0 equiv.), and DMSO (2.5 mL) at 0 °C, and the mixture was stirred for 10 h at 20 °C. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with H_2O (3 × 25 mL). The organic layer was then dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 3:1).

Ethyl (1*R,2*S**)-2-(*tert*-Butoxycarbonylamino)-5-oxocyclohexanecarboxylate (30):** A white solid (76%), m.p. 134–137 °C. R_f = 0.45 (*n*-hexane/EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, J = 7.15 Hz, 3 H, CH_3), 1.44 (s, 9 H, *t*Bu), 2.05–2.14 (m, 2 H, CH_2), 2.40–2.60 (m, 3 H, CH_2), 2.72–2.79 (m, 1 H, CH_2), 3.19–3.26 (m, 1 H, 1-H), 4.19–4.30 (m, 3 H, OCH_2, 2-H), 5.20 (br. s, 1 H, NH) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 15.0, 28.7, 29.1, 38.5, 41.1, 45.6, 48.5, 61.7, 80.3, 155.5, 172.6, 207.6 ppm. $C_{14}H_{23}NO_5$ (285.34): calcd. C 58.93, H 8.12, N 4.91; found C 58.61, H 7.76, N 4.60.

Ethyl (1*S,2*S**)-2-(*tert*-Butoxycarbonylamino)-5-oxocyclohexanecarboxylate (31):** A white solid (73%), m.p. 117–120 °C. R_f = 0.40 (*n*-hexane/EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.15 Hz, 3 H, CH_3), 1.45 (s, 9 H, *t*Bu), 1.70–1.81 (m, 1 H, CH_2), 2.26–2.60 (m, 4 H, CH_2), 2.70–2.79 (m, 2 H, CH_2, 1-H), 4.08–4.24 (m, 3 H, OCH_2, 2-H), 4.70 (br. s, 1 H, NH) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.5, 28.7, 31.5, 39.2, 41.7, 48.8, 50.2, 61.7, 80.5, 155.3, 172.1, 207.8 ppm. $C_{14}H_{23}NO_5$ (285.34): calcd. C 58.93, H 8.12, N 4.91; found C 58.60, H 7.79, N 4.63.

General Procedure for Fluorination of Keto-Amino Esters 26 and 27: To a solution of amino ester **26** or **27** (1.5 mmol) in CH_2Cl_2 (12 mL) was added Deoxo-Fluor (50% in toluene, 1.5 equiv.) and one drop of EtOH at 0 °C. Stirring was continued at this temperature for 8 h. The mixture was then diluted with CH_2Cl_2 (25 mL), and the organic phase was washed with an aqueous solution of $NaHCO_3$. The organic layer was dried with Na_2SO_4 and concentrated, and the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 4:1).

Ethyl (1*R,2*S**)-2-(*tert*-Butoxycarbonylamino)-5,5-difluorocyclohexanecarboxylate (32):** A white solid (36%), m.p. 98–100 °C. R_f = 0.65 (*n*-hexane/EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.20 Hz, 3 H, CH_3), 1.43 (s, 9 H, *t*Bu), 1.79–1.88 (m, 1 H, CH_2), 1.90–2.08 (m, 2 H, CH_2), 2.10–2.21 (m, 2 H, CH_2), 2.31–2.44 (m, 1 H, CH_2), 2.94–2.99 (m, 1 H, 1-H), 4.03–4.10 (m, 1 H, 2-H), 4.16–4.24 (m, 2 H, OCH_2), 5.23 (br. s, 1 H, NH) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.4, 26.8, 28.7, 31.1, 33.9, 42.9, 47.5, 61.4, 80.1, 122.6, 155.6, 172.0 ppm. $C_{14}H_{23}F_2NO_4$ (307.34): calcd. C 54.71, H 7.54, N 4.56; found C 55.06, H 7.20, N 4.23.

Ethyl (1*S,2*S**)-2-(*tert*-Butoxycarbonylamino)-5,5-difluorocyclohexanecarboxylate (33):** A white solid (37%), m.p. 97–99 °C. R_f = 0.60 (*n*-hexane/EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.20 Hz, 3 H, CH_3), 1.41 (s, 9 H, *t*Bu), 1.50–1.61 (m, 1 H, CH_2), 1.79–1.96 (m, 1 H, CH_2), 2.06–2.17 (m, 3 H, CH_2), 2.22–2.31 (m, 1 H, CH_2), 2.56–2.62 (m, 1 H, 1-H), 3.70–3.81 (m, 1 H, 2-H), 4.13–4.20 (2 H, OCH_2), 4.47 (br. s, 1 H, NH) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.5, 22.5, 28.7, 32.6, 35.6, 46.0, 49.6, 61.6, 80.5, 119.4, 155.2, 172.5 ppm. $C_{14}H_{23}F_2NO_4$ (307.34): calcd. C 54.71, H 7.54, N 4.56; found C 54.40, H 7.21, N 4.79.

Characterization of the Enantiomers: The ^{1}H NMR spectroscopic data of the enantiomeric compounds were the same as those of the racemic compounds.

(1*R*,6*S*)-6-(*tert*-Butoxycarbonylamino)cyclohex-3-enecarboxylic Acid [(–)-1]: A white solid (76%), m.p. 75–78 °C (*n*-hexane). $[\alpha]_D^{25}$ = –22.6 (c = 4.8, $CHCl_3$).

***tert*-Butyl (1*R*,2*S*,4*S*,5*S*)-4-Iodo-7-oxo-6-oxabicyclo[3.2.1]octan-2-ylcarbamate [(–)-24]:** A white solid (79%; for the racemic compound, see ref.[9]), m.p. 179–180 °C (*n*-hexane). $[\alpha]_D^{25}$ = –58.1 (c = 1.7, $CHCl_3$).

***tert*-Butyl (1*R*,2*S*,5*S*)-7-Oxo-6-oxabicyclo[3.2.1]oct-3-en-2-ylcarbamate [(–)-25]:** A white solid (69%; for the racemic compound, see ref.[9]), m.p. 144–146 °C (*n*-hexane). $[\alpha]_D^{25}$ = –35.4 (*c* = 1.45, $CHCl_3$).

Ethyl (1*R*,2*S*,5*S*)-2-(*tert*-Butoxycarbonylamino)-5-hydroxycyclohex-3-enecarboxylate [(+)-2]: (see also ref.[9]) A white solid (70%), m.p. 86–88 °C (*n*-hexane). $[\alpha]_D^{25}$ = +53.5 (*c* = 0.9, $CHCl_3$).

Ethyl (1*S*,2*S*,5*S*)-2-(*tert*-Butoxycarbonylamino)-5-hydroxycyclohex-3-enecarboxylate [(+)-10]: (see also ref.[9]) A white solid (66%), m.p. 106–108 °C (*n*-hexane). $[\alpha]_D^{25}$ = +31.3 (*c* = 1, $CHCl_3$).

Ethyl (1*R*,2*S*,5*R*)-2-(*tert*-Butoxycarbonylamino)-5-hydroxycyclohexanecarboxylate [(–)-3]: A colorless oil (83%). $[\alpha]_D^{25}$ = –11.2 (*c* = 0.55, $CHCl_3$).

Ethyl (1*S*,2*S*,5*R*)-2-(*tert*-Butoxycarbonylamino)-5-hydroxycyclohexanecarboxylate [(+)-11]: A colorless oil (81%). $[\alpha]_D^{25}$ = +11.1 (*c* = 0.75, $CHCl_3$).

Ethyl (1*R*,2*S*,5*S*)-2-(*tert*-Butoxycarbonylamino)-5-fluorocyclohexanecarboxylate [(–)-4]:[8] A white solid (43%, 98%*ee*), m.p. 60–63 °C (*n*-hexane). $[\alpha]_D^{25}$ = –2.0 (*c* = 0.465, $CHCl_3$).

Ethyl (1*S*,2*S*,5*S*)-2-(*tert*-Butoxycarbonylamino)-5-fluorocyclohexanecarboxylate [(+)-12]: A white solid (45%, 98%*ee*) m.p. 69–72 °C (*n*-hexane). $[\alpha]_D^{25}$ = +11.4 (*c* = 1.735, $CHCl_3$).

(1*S*,2*S*)-2-(*tert*-Butoxycarbonylamino)cyclohex-3-enecarboxylic Acid [(+)-16]: A white solid (79%), m.p. 125–126 °C (*n*-hexane/EtOAc). $[\alpha]_D^{25}$ = +22.7 (*c* = 0.55, EtOH).

***tert*-Butyl (1*S*,2*S*,4*R*,5*R*)-4-Iodo-7-oxo-6-oxabicyclo[3.2.1]octan-2-ylcarbamate [(+)-28]:** A white solid (86%), m.p. 159–161 °C (*n*-hexane/EtOAc). $[\alpha]_D^{25}$ = +20.2 (*c* = 0.75, EtOH).

***tert*-Butyl (1*S*,2*S*,5*R*)-7-Oxo-6-oxabicyclo[3.2.1]oct-3-en-2-ylcarbamate [(+)-29]:** A white solid (69%), m.p. 146–149 °C (*n*-hexane/EtOAc). $[\alpha]_D^{25}$ = +177.2 (*c* = 0.325, EtOH).

Ethyl (1*S*,2*S*,5*R*)-2-(*tert*-Butoxycarbonylamino)-5-hydroxycyclohex-3-enecarboxylate [(+)-17]: (see also ref.[9]). A white solid (68%), m.p. 140–143 °C (*n*-hexane/EtOAc). $[\alpha]_D^{25}$ = +118.3 (*c* = 0.5, EtOH).

Ethyl (1*S*,2*S*,5*S*)-2-(*tert*-Butoxycarbonylamino)-5-hydroxycyclohexanecarboxylate [(+)-18]: A white solid (79%), m.p. 126–129 °C (*n*-hexane/EtOAc). $[\alpha]_D^{25}$ = +3.6 (*c* = 0.675, EtOH).

Ethyl (1*S*,2*S*,5*R*)-2-(*tert*-butoxycarbonylamino)-5-fluorocyclohexanecarboxylate [(+)-19]: A white solid (41%, 94%*ee*), m.p. 80–82 °C (*n*-hexane/EtOAc). $[\alpha]_D^{25}$ = +8.2 (*c* = 0.6, EtOH).

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