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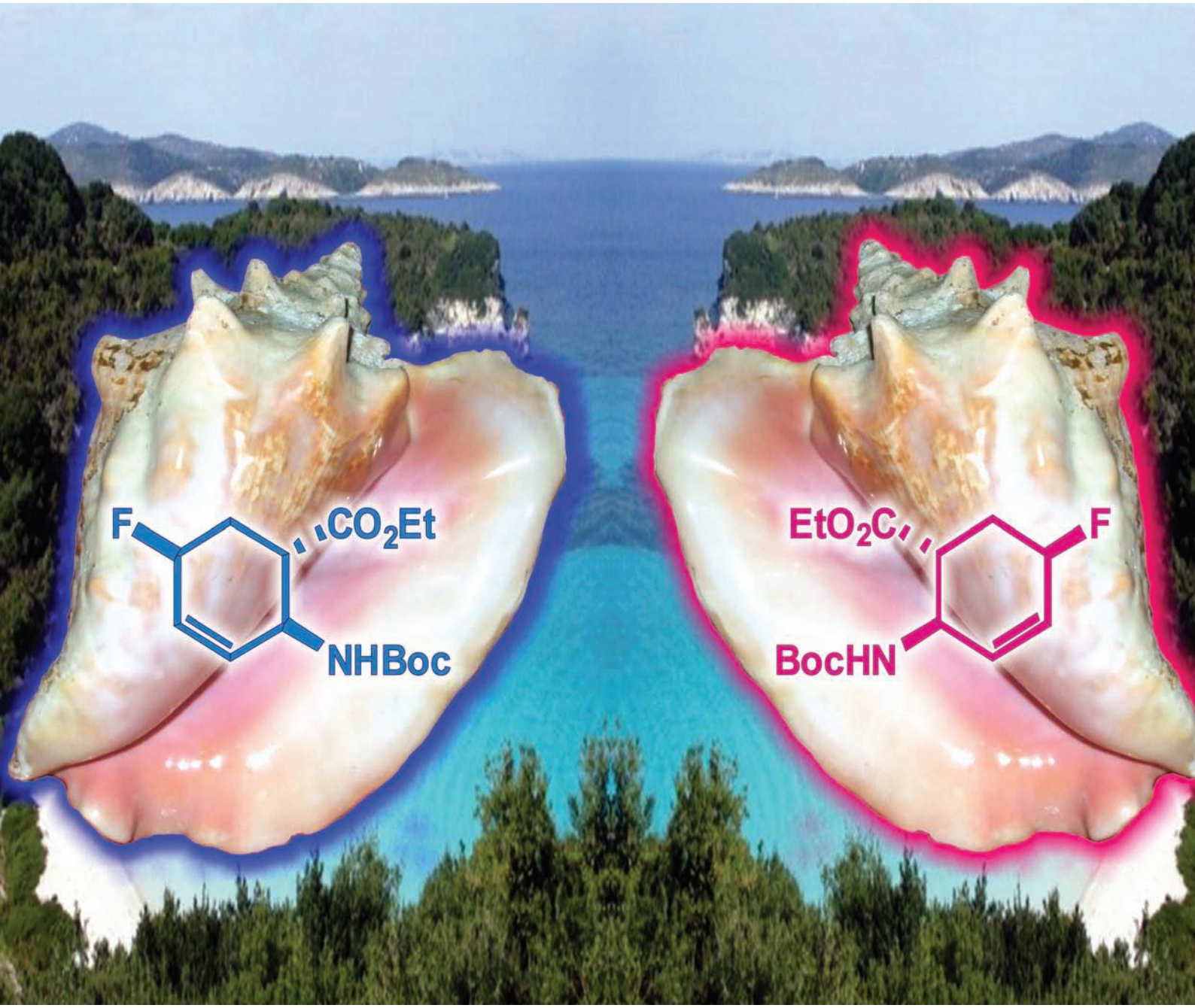

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PAPER

Regio- and diastereoselective fluorination of alicyclic β-amino acids†

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A regio- and stereoselective approach to fluorinated β-aminocyclohexene or cyclohexane esters has been developed, starting from a bicyclic β-lactam (**1**). The procedure involves six or seven steps, based on regio- and stereoselective iodolactonization, lactone opening and hydroxy–fluorine exchange. The method has been extended to the synthesis of fluorinated amino ester enantiomers.

Introduction

Introduction of fluorine, thanks to its unique properties, into organic molecules has become a very attractive area of synthetic and medicinal chemistry. Although fluorine is virtually absent in biologically active natural products, its presence in many compounds with important pharmacological properties, *e.g.* drugs and agrochemicals, has led to an enormous increase in fluorine interest in organic chemistry in the past 20 years. The role of fluorine in medicinal chemistry and drug design is reflected in the increasing number of fluorine-containing drugs on the market (more than 20%). Based on a score of unique characteristics of the fluorine atom (small steric size and high electronegativity) and of the C–F bond (high bond energy and low polarizability), introduction of a fluorine atom into an organic molecule generates a series of changes in properties such as polar hydrophobicity, high dipole moment and effects on basicity reactivity and metabolic stability. Moreover, the introduction of one or more fluorine atoms into biologically active molecules may generate profound and remarkable changes in their biological properties.[1]

Among the large family of bioactive fluorinated compounds, fluorinated amino acids[2] and peptides[3] are of value in medicinal chemistry as enzyme inhibitors, antitumour agents and antibiotics. Owing to the special characteristics of fluorine, the chemistry of fluorinated cyclic amino acids is a very interesting area. In spite of the great potential of cyclic amino acids, only few cyclic fluorinated derivatives have been reported so far, among either α-amino acids[2a,4] or γ-amino acids (conformationally restricted fluorinated GABA analogues).[2a,5]

Furthermore, although cyclic β-amino acids have recently generated increasing interest,[6] somewhat surprisingly for us, only few fluorinated cyclic β-amino acids have been synthesized so far.[2f,7]

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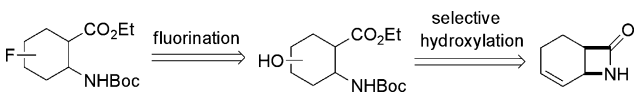
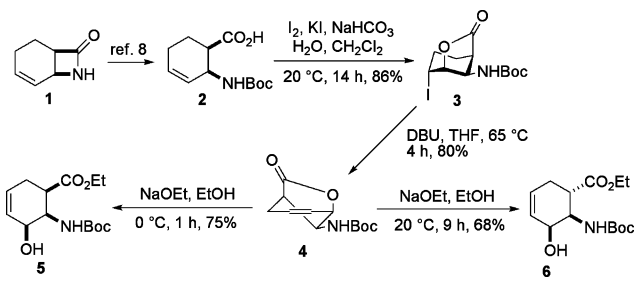
Results and discussion

Our present aim was to develop a stereo- and regioselective synthetic route to mono- and difluorinated β-aminocyclohexancarboxylates. The stereo- and regioselective introduction of a fluorine atom onto the cycloalkane skeleton of a β-amino acid was accomplished by selective hydroxylation, followed by hydroxy–fluorine exchange, using either diethylaminosulfur trifluoride (DAST) or bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor) as fluorinating agent (Scheme 1). A hydroxy function was stereo- and regioselectively introduced onto the skeleton of an alicyclic β-amino acid, with selective iodolactonization as key step. The unsaturated cyclic N-Boc-protected amino acid **2**, obtained from bicyclic β-lactam **1** was subjected to iodolactonization in the presence of KI/I_2 in a slightly alkaline medium, to furnish lactone **3** selectively (Scheme 2).[8]



Scheme 1 Retrosynthetic scheme for the regio- and stereoselective synthesis of fluorinated β-amino esters.



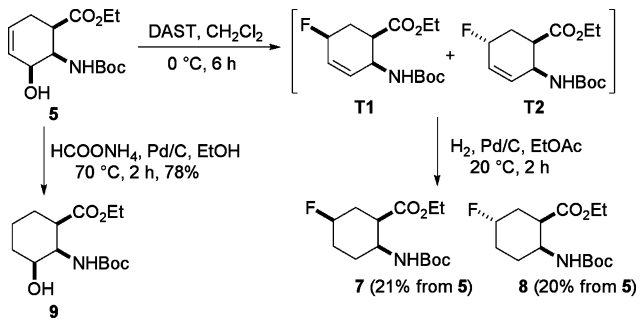
Scheme 2 Synthesis of hydroxylated β-amino ester diastereoisomers **5** and **6**.

Subsequently, base-mediated dehydroiodination of iodolactone **3** in the presence of DBU in refluxing THF afforded unsaturated lactone **4**. Lactone ring-opening with NaOEt in EtOH at 0 °C for 1 h furnished the *all-cis*-hydroxylated β-amino ester **5** in 75% yield. The similar transformation of **4** at 20 °C for 9 h

resulted in epimerization at C-1, to afford **6**, a diastereoisomer of **5** (Scheme 2).

Diastereoisomers **5** and **6** were next subjected to fluorination based on hydroxy–fluorine exchange methodology, with the use of DAST or Deoxofluor. When treated with DAST in CH_2Cl_2 at 0 °C, **5** gave an oily mixture of two fluorinated products (**T1** and **T2**) in approximately 1 : 1 ratio (^{1}H-NMR spectroscopy), which could not be separated by flash chromatography.

Catalytic hydrogenation of this mixture in EtOAc and column chromatographic separation of the products on silica gel with n-hexane–EtOAc 9 : 1 as eluent furnished two β-aminocarboxylate diastereoisomers (**7** and **8**), with the fluorine atom on position 5 of the cyclohexane ring (Scheme 3). The structures of **7** and **8** were determined by 2D NMR and X-ray analysis (Fig. 1).



Scheme 3 Synthesis of fluorinated β-amino esters **7** and **8**.

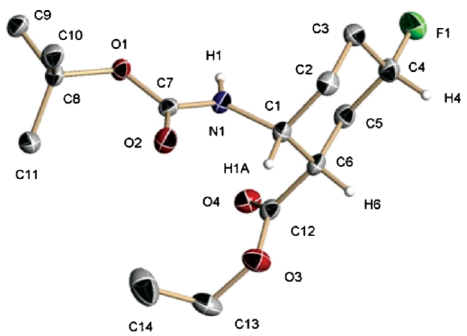
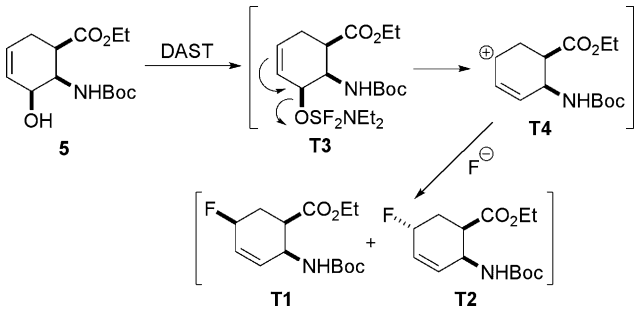


Fig. 1 ORTEP diagram of **7**.

These experimental results suggested that, in contrast with the generally observed S_N2 mechanism of hydroxy–fluorine exchange, **5** undergoes an allylic rearrangement to **T4** in the presence of DAST followed by fluoride attack at C-5 through an S_N1 process (Scheme 4).

In attempts to synthetize 3-fluorinated β-amino acids the *all-cis*-3-hydroxylated amino ester **5** was first saturated to **9** (Fig. 2). However, treatment of **9** with either DAST or Deoxofluor did, not result in any fluorinated derivative, but only an inseparable and unidentified mixture of elimination (detected by ^{1}H NMR of the mixture) products (Scheme 3). The reason for this unexpected result is not yet known, probably stereochemical aspects contribute to this phenomenon.

Fluorination of **6** upon treatment with either DAST or Deoxofluor gave not the expected 3-fluorinated amino ester (S_N2 product), but the 5-fluorinated 2-aminocyclohexenecarboxylate **10** (Scheme 5, Fig. 3). This transformation may be explained by attack



Scheme 4 Possible route to fluorinated amino esters **7** and **8**.

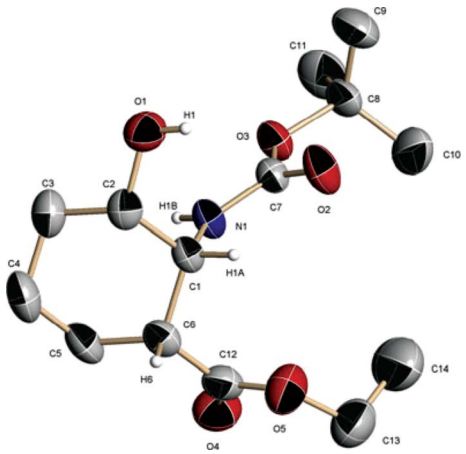


Fig. 2 ORTEP diagram of **9**.

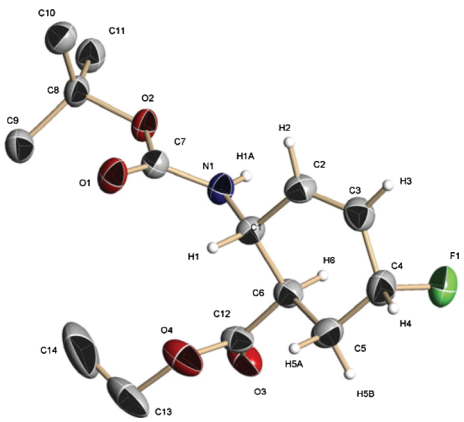


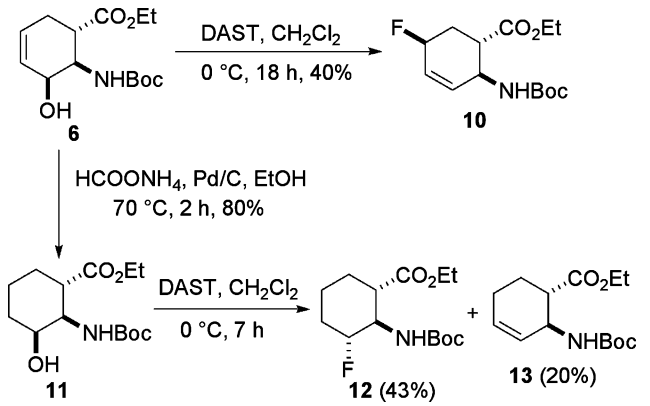
Fig. 3 ORTEP diagram of **10**.

of the fluoride anion on the sp^2 C-atom at position 5 of **6**, with simultaneous displacement of the hydroxy function according to an S_N2' mechanism (Scheme 6).

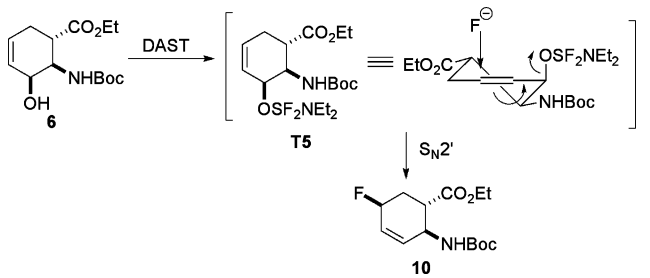
In contrast with its *all-cis* counterpart (**9**) (Scheme 3), fluorination of **11** in the presence of DAST in CH_2Cl_2 at 0 °C furnished 3-fluoro-2-aminocyclohexanecarboxylate **12** in 43% isolated yield; it was separated from the side-product **13** by flash chromatography (Scheme 5).

The above-presented synthetic route to fluorinated β-aminocyclohexanecarboxylates could be extended towards the synthesis of these compounds in enantiomerically pure form.

Enantiomerically pure amino acid **(+)-14** was synthetized through CAL-B-catalysed ring cleavage of the corresponding

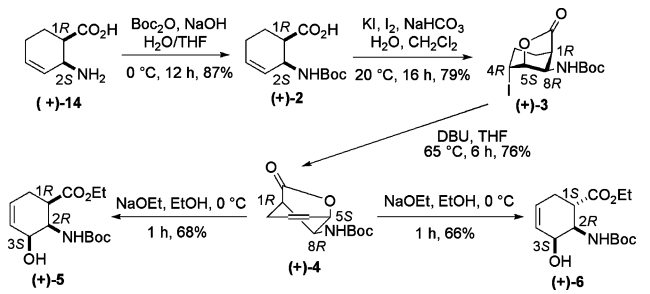


Scheme 5 Synthesis of fluorinated β-amino esters **10** and **12**.



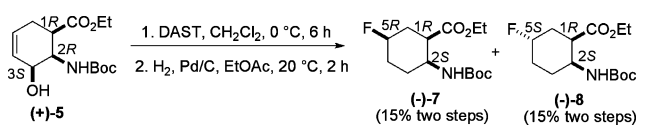
Scheme 6 Possible route to fluorinated amino ester **10**.

racemic β-lactam **1**, by the method previously described.[9] Amino acid **(+)-14** was converted then (in the same way as for the racemic substances) through the corresponding optically pure lactone **(+)-4** into hydroxylated amino esters **(+)-5** and **(+)-6** (Scheme 7).



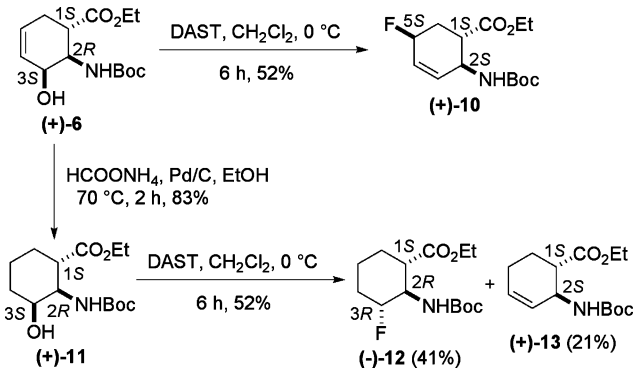
Scheme 7 Synthesis of hydroxylated amino ester enantiomers **(+)-5** and **(+)-6**.

Hydroxylated amino ester enantiomer **(+)-5** was transformed by treatment with DAST, followed by hydrogenation of the obtained mixture into optically pure fluorinated aminocarboxylates **(–)-7** and **(–)-8** (15% overall yield for the two steps; Scheme 8).



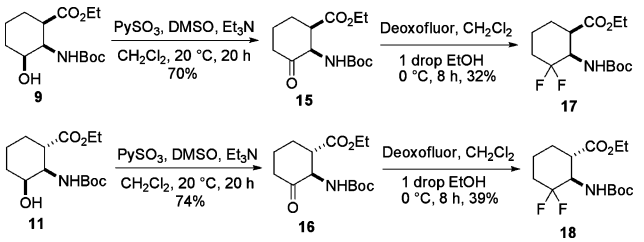
Scheme 8 Synthesis of fluorinated amino ester enantiomers **(–)-7** and **(–)-8**.

Fluorination of **(+)-6** gave enantiopure 5-fluorinated amino ester **(+)-10**, while saturation to **(+)-11**, followed by treatment with DAST, resulted in the enantiomerically pure 3-fluorinated aminocarboxylate **(–)-12** in 41% yield (Scheme 9).



Scheme 9 Synthesis of fluorinated amino ester enantiomers **(+)-10** and **(–)-12**.

Selective hydroxylation of amino esters permits the synthesis of geminal difluorinated amino derivatives *via* the corresponding keto-aminocarboxylates. For this purpose, hydroxy amino esters **9** and **11** were oxidized with sulfur trioxide-pyridine complex in the presence of Et_3N, in DMSO to give the corresponding 3-keto-2-aminocarboxylates **15** and **16** in good yields (Scheme 10, Fig. 4).



Scheme 10 Synthesis of difluorinated β-amino esters **17** and **18**.

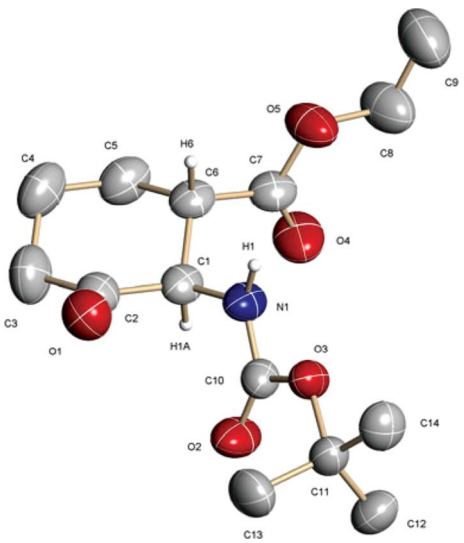


Fig. 4 ORTEP diagram of 16.

On treatment with Deoxofluor and 1 drop of EtOH in CH_2Cl_2, amino esters **15** and **16** underwent fluorination involving

oxo–difluoro exchange to afford the desired difluorinated amino esters **17** and **18** in moderate yields (Scheme 10).

Conclusions

In conclusion, a selective approach has been developed for the introduction of a fluorine atom onto the cyclohexane ring of a cyclic β-amino acid *via* selective hydroxylation and hydroxy–fluorine exchange. This method allowed the synthesis of the enantiomers of novel monofluorinated β-aminocarboxylates and geminal difluorinated derivatives.

Experimental section

General procedure for dehydroiodination of iodolactone

DBU (2.1 equiv, 18.9 mmol) was added to a solution of iodolactone **3** (9 mmol) in THF (40 mL), and the mixture was stirred at 65 °C for 4 h. The solution was then concentrated under reduced pressure and the residue was extracted with EtOAc (100 mL). The organic layer was washed with H_2O (3 × 50 mL), dried (Na_2SO_4) and concentrated under vacuum. The residue was crystallized from n-hexane–EtOAc, giving a white solid.

tert-Butyl (1*R**,5*S**,8*R**)-7-oxo-6-oxabicyclo[3.2.1]oct-3-en-8-ylcarbamate (4)

A white solid, mp 146–147 °C. Yield: 80%. (R_f 0.45, n-hexane–EtOAc 2 : 1). ^{1}H NMR (400 MHz, DMSO): δ = 1.43 (s, 9H, *t*Bu), 2.33–2.41 (m, 1H, CH_2), 2.60–2.67 (m, 1H, CH_2), 2.78–2.82 (m, 1H, H-1), 3.85–3.90 (m, 1H, H-8), 4.68–4.74 (m, 1H H-5), 5.88–5.95 (m, 1H, H-2), 6.24–6.30 (m, 1H, H-3), 7.58 (brs, 1H, N-H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 28.7, 30.1, 44.6, 57.2, 77.6, 81.5, 128.4, 131.3, 155.4, 172.0. Anal. Calcd. for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.45; H, 6.90; N, 5.58.

General procedure for ring opening of bicyclic lactone 4

NaOEt (1.2 equiv, 3.6 mmol) was added to a solution of unsaturated lactone **4** (3 mmol) in anhydrous EtOH (20 mL) at 0 °C, and the reaction mixture was stirred further at the temperature and for the time indicated in the text. The EtOH was then removed under reduced pressure at 40 °C and the residue was extracted with CH_2Cl_2 (40 mL). The organic layer was washed with H_2O (2 × 20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (n-hexane–EtOAc).

Ethyl (1*R**,2*R**,3*S**)-2-(*tert*-butoxycarbonylamino)-3-hydroxycyclohex-4-enecarboxylate (5)

A colourless oil. Yield: 75%. (R_f 0.45, n-hexane–EtOAc 1 : 1). ^{1}H NMR (400 MHz, DMSO): δ = 1.19 (t, 3H, CH_3, J = 7.20 Hz), 1.38 (s, 9H, *t*Bu), 2.00–2.08 (m, 1H, CH_2), 2.37–2.44 (m, 1H, CH_2), 2.79–2.88 (m, 1H, H-1), 3.98–4.06 (m, 2H, OCH_2), 4.15–4.20 (m, 1H, H-2), 4.21–4.27 (m, 1H, H-3), 4.82 (brs, 1H, O-H), 5.38–5.42 (m, 1H, H-5), 5.58 (brs, 1H, N-H), 5.60–5.64 (m, 1H, H-4). ^{13}C NMR (400 MHz, DMSO): δ = 14.8, 23.8, 29.0, 40.6, 51.7, 60.6, 66.9, 78.6, 127.5, 131.8, 156.4, 173.1. Anal. Calcd. for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.65; H, 7.86; N, 5.25.

Ethyl (1*S**,2*R**,3*S**)-2-(*tert*-butoxycarbonylamino)-3-hydroxycyclohex-4-enecarboxylate (6)

A colourless oil. Yield: 68%. (R_f 0.40, n-hexane–EtOAc 1 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, 3H, CH_3, J = 7.10 Hz), 1.42 (s, 9H, *t*Bu), 2.38–2.43 (m, 1H, CH_2), 2.55–2.60 (m, 1H, CH_2), 2.77–2.82 (m, 1H, H-1), 3.99–4.05 (m, 1H, H-2), 4.17–4.22 (m, 3H, H-3 and OCH_2), 5.10 (brs, 1H, N–H), 5.82–5.98 (m, 2H, H-4 and H-5). ^{13}C NMR (400 MHz, DMSO): δ = 14.6, 28.6, 28.7, 41.3, 52.5, 61.3, 65.4, 80.5, 127.2, 129.9, 155.6, 172.0. Anal. Calcd. for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.61; H, 7.80; N, 4.60.

General procedure for the reduction of 5 or 6

$HCOONH_4$ (8 mmol, 5 equiv) and 10% Pd/C (90 mg) were added to a solution of hydroxy amino ester **5** or **6** (1.5 mmol) in EtOH (20 mL) and the mixture was stirred at 75 °C. After 1 h the solids were filtered off, and the filtrate was concentrated and purified by flash chromatography on silica gel (n-hexane–EtOAc 1 : 1).

Ethyl (1*R**,2*R**,3*S**)-2-(*tert*-butoxycarbonylamino)-3-hydroxycyclohexanecarboxylate (9)

A white solid, mp 92–95 °C. Yield: 78%. (R_f 0.50, n-hexane–EtOAc 2 : 1). ^{1}H NMR (400 MHz, DMSO): δ = 1.24 (t, 3H, CH_3, J = 7.10 Hz), 1.32–1.40 (m, 1H, CH_2), 1.46 (s, 9H, *t*Bu), 1.65–1.78 (m, 5H, CH_2), 2.88–2.92 (m, 1H, H-1), 3.82–3.86 (m, 1H, H-2), 4.02–4.08 (m, 1H, H-3), 4.13–4.20 (m, 2H, OCH_2), 5.22 (brs, 1H, N–H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.5, 18.8, 25.2, 28.7, 31.1, 44.5, 52.4, 61.5, 70.4, 80.5, 150.2, 170.6. Anal. Calcd. for $C_{14}H_{25}NO_5$: C, 58.52; H, 8.77; N, 4.87. Found: C, 58.22; H, 8.99; N, 4.53.

Ethyl (1*S**,2*R**,3*S**)-2-(*tert*-butoxycarbonylamino)-3-hydroxycyclohexanecarboxylate (11)

A white solid, mp 56–58 °C. Yield: 80%. (R_f 0.50, n-hexane–EtOAc 2 : 1). ^{1}H NMR (400 MHz, DMSO): δ = 1.22 (t, 3H, CH_3, J = 7.15 Hz), 1.41 (s, 9H, *t*Bu), 1.50–1.65 (m, 4H, CH_2), 1.82–1.95 (m, 2H, CH_2). 2.66–2.73 (m, 1H, H-1), 3.73–3.80 (m, 1H, H-2), 4.08–4.17 (m, 3H, H-3 and OCH_2), 5.00 (brs, 1H, N–H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.6, 18.5, 28.5, 28.7, 32.0, 44.3, 54.8, 60.9, 68.9, 80.5, 152.3, 174.6. Anal. Calcd. for $C_{14}H_{25}NO_5$: C, 58.52; H, 8.77; N, 4.87. Found: C, 58.71; H, 8.49; N, 4.59.

General procedure for reduction of fluorinated amino esters (T1 and T2) with a cyclohexene skeleton

10% Pd/C (60 mg) was added to a solution of fluorinated amino ester mixture (**T1** and **T2**) (1 mmol) in EtOAc (15 mL) and the mixture was stirred under H_2 at 20 °C. After 1 h the solids were filtered off, and the filtrate was concentrated and purified by flash chromatography on silica gel (n-hexane–EtOAc 1 : 1).

General procedure for fluorination

DAST or Deoxofluor in 50% toluene (1.3 equiv) was added at 0 °C to a solution of hydroxy amino ester **5**, **6**, **9** or **11** (0.5 mmol) in CH_2Cl_2 (5 mL) under an Ar atmosphere and the solution was stirred for the time indicated. 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 (Na_2SO_4) and concentrated. The crude product was purified on flash chromatography on silica gel (n-hexane–EtOAc 9 : 1).

Ethyl (1*R**,2*S**,5*R**)-2-(*tert*-butoxycarbonylamino)-5-fluorocyclohexanecarboxylate (7)

A white solid, mp 95–99 °C (n-hexane). Yield: 21% (from **5**) (R_f 0.55, n-hexane–EtOAc 4 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, 3H, CH_3, J = 7.15 Hz), 1.43 (s, 9H, *t*Bu), 1.59–1.80 (m, 2H, CH_2), 1.82–2.00 (m, 2H, CH_2), 2.10–2.21 (m, 1H, CH_2), 2.39–2.44 (m, 1H, CH_2), 2.72–2.77 (m, 1H, H-1), 3.82–3.93 (m, 1H, H-2), 4.16–4.23 (m, 2H, OCH_2), 4.62–4.80 (m, 1H, H-5), 5.56 (brs, 1H, N–H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.4, 25.4, 28.8, 29.7, 32.7, 42.1, 48.3, 60.9, 79.9, 87.8, 89.5, 155.2, 172.5. Anal. Calcd. for $C_{14}H_{24}FNO_4$: C, 58.11; H, 8.36; N, 4.84. Found: C, 58.36; H, 7.99; N, 4.50.

Ethyl (1*R**,2*S**,5*S**)-2-(*tert*-butoxycarbonylamino)-5-fluorocyclohexanecarboxylate (8)

A white solid, mp 64–66 °C (n-hexane). Yield: 20% (from **5**) (R_f 0.6, n-hexane–EtOAc 4 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (t, 3H, CH_3, J = 7.15 Hz), 1.39 (s, 9H, *t*Bu), 1.62–2.20 (m, 6H, CH_2), 2-91–2.99 (m, 1H, H-1), 3.95–4.02 (m, 1H, H-2), 4.04–4.09 (m, 2H, OCH_2), 4.57–4.70 (m, 1H, H-5), 4.99 (brs, 1H, N–H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.2, 25.6, 25.7, 28.4, 41.5, 44.7, 47.9, 60.8, 79.5, 86.8, 89.1, 155.2, 173.5. Anal. Calcd. for $C_{14}H_{24}FNO_4$: C, 58.11; H, 8.36; N, 4.84. Found: C, 58.40; H, 8.01; N, 5.19.

Ethyl (1*S**,2*S**,5*S**)-2-(*tert*-butoxycarbonyl)-5-fluorocyclohex-3-enecarboxylate (10)

A white solid, mp 128–130 °C (n-hexane). Yield: 40% (R_f 0.6, n-hexane–EtOAc 3 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, 3H, CH_3, J = 7.15 Hz), 1.46 (s, 9H, *t*Bu), 2.00–2.10 (m, 1H, CH_2), 2.12–2.18 (m, 1H, CH_2), 2.55–2.71 (m, 1H, H-1), 4.06–4.12 (m, 2H, OCH_2), 4.38–4.46 (m, 1H, H-2), 4.67 (brs, 1H, N-H), 4.88–5.09(m, 1H, H-5), 5.88–6.00 (m, 2H, H-3 and H-4). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.6, 28.7, 31.2, 42.5, 49.5, 61.5, 80.2, 81.9, 84.1, 125.7, 135.8, 155.4, 173.4. Anal. Calcd. for $C_{14}H_{22}FNO_4$: C, 58.52; H, 7.72; N, 4.87. Found: C, 58.17; H, 8.03; N, 4.51.

Ethyl (1*S**,2*R**,3*R**)-2-(*tert*-butoxycarbonylamino)-3-fluorocyclohexanecarboxylate (12)

A white solid, mp 94–96 °C (n-hexane). Yield: 43% (R_f 0.65, n-hexane–EtOAc 3 : 1). ^{1}H NMR (400 MHz, DMSO): δ = 1.23 (t, 3H, CH_3, J = 7.15 Hz), 1.32–1.40 (m, 2H, CH_2), 1.41 (s, 9H, *t*Bu), 1.42–1.51 (m, 1H, CH_2), 1.60–1.68 (m, 2H, CH_2), 2.02–2.10 (m, 1H, CH_2), 2.40–2.48 (m, 1H, H-1), 3.52–3.57 (m, 1H, H-2), 3.99–4.09 (m, 2H, OCH_2), 4.18–4.46 (m, 1H, H-3), 6.92 (brs, 1H, N–H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.6, 22.6, 28.7, 30.1, 31.8, 48.1, 56.6, 61.2, 80.8, 89.0, 91.0, 154.5, 170.3. Anal. Calcd. for $C_{14}H_{24}FNO_4$: C, 58.11; H, 8.36; N, 4.84. Found: C, 57.80; H, 8.01; N, 4.53.

Ethyl (1*S**,2*S**)-2-(*tert*-butoxycarbonylamino)cyclohex-3-enecarboxylate (13)

A white solid, mp 55–57 °C (n-hexane). Yield: 20% (R_f 0.7, n-hexane–EtOAc 3 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, 3H, CH_3, J = 7.15 Hz), 1.42 (s, 9H, *t*Bu), 1.83–1.90 (m, 2H, CH_2), 2.05–2.10 (m, 2H, CH_2), 2.53–2.58 (m, 1H, H-1), 4.13–4.19 (m, 2H, OCH_2), 4.41–4.47 (m, 1H, H-2), 4.58 (brs, 1H, N–H), 5.60–5.65 (m, 1H, H-4), 5.79–5.86 (m, 1H, H-3). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.6, 23.9, 24.0, 28.7, 46.5, 48.7, 60.9, 80.7, 128.2, 129.5, 155.4, 174.2. Anal. Calcd. for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.08; H, 8.98; N, 4.91.

Characterization of enantiomers

The ee value for **(–)-7** was determined by gas chromatography on a Chromopack Chiralsil-L-Val column (25 m) {[100 °C for 7 min → 190 °C (temperature increase 5 °C min-1); 70 kPa; retention time (min): 19.48 (antipode: 19.38). The ee values for **(–)-8**, **(–)-12** and **(+)-10** were determined by gas chromatography on a Chromopack Chirasil-Dex CB column (25 m) {[120 °C for 7 min → 190 °C (temperature increase 5 °C min-1); 70 kPa; retention times (min): **(–)-8**: 20.58 (antipode 20.66), **(–)-12**: 22.29 (antipode 22.77), **(+)-10**: 22.36 (antipode 22.46).

The NMR spectra of the enantiomeric compounds were the same as those for the racemic compounds.

(1*R*,2*S*)-2-(*tert*-Butoxycarbonylamino)cyclohex-3-enecarboxylic acid [(–)-2]

A white solid, mp 117–118 °C (n-hexane). Yield: 87%. $[\alpha]_D^{25}$ = +22.8 (*c* 0.55, EtOH).

tert-Butyl (1*R*,4*R*,5*R*,8*R*)-4-iodo-7-oxo-6-oxabicyclo[3.2.1]octan-8-ylcarbamate [(–)-3]

A white solid, mp 161–163 °C (n-hexane). Yield: 79%. $[\alpha]_D^{25}$ = +16 (*c* 1.435, EtOH).

tert-Butyl (1*R*,5*R*,8*S*)-7-oxo-6-oxabicyclo[3.2.1]oct-3-en-8-ylcarbamate [(–)-4]

A white solid, mp 144–145 °C (n-hexane). Yield: 76%. $[\alpha]_D^{25}$ = +113 (*c* 0.38, EtOH).

Ethyl (1*R*,2*R*,3*S*)-2-(*tert*-butoxycarbonylamino)-3-hydroxycyclohex-4-enecarboxylate [(–)-5]

A colourless oil. Yield: 68%. $[\alpha]_D^{25}$ = +43.6 (*c* 0.515, EtOH).

Ethyl (1*S*,2*R*,3*S*)-2-(*tert*-butoxycarbonylamino)-3-hydroxycyclohex-4-enecarboxylate [(–)-6]

A colourless oil. Yield: 66%. $[\alpha]_D^{25}$ = +563 (*c* 0.305, EtOH).

Ethyl (1*S*,2*S*,3*R*)-2-(*tert*-butoxycarbonylamino)-3-hydroxycyclohexanecarboxylate [(–)-11]

A white solid, mp 55–58 °C. Yield: 83%. $[\alpha]_D^{25}$ = +58.4 (*c* 0.635, EtOH).

Ethyl (1*S*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohex-3-enecarboxylate [(−)-13]

A white solid, mp 58–61 °C (n-hexane). Yield: 21%. $[\alpha]_D^{25} = +65.2$ (*c* 0.5, EtOH).

Ethyl (1*R*,2*S*,5*R*)-2-(*tert*-butoxycarbonylamino)-5-fluorocyclohexanecarboxylate [(−)-7]

A white solid, mp 94–96 °C (n-hexane). Yield: 15% (two steps). ee > 98%, $[\alpha]_D^{25} = -10.8$ (*c* 0.59, EtOH).

Ethyl (1*R*,2*S*,5*S*)-2-(*tert*-butoxycarbonylamino)-5-fluorocyclohexanecarboxylate [(−)-8]

A white solid, mp 62–63 °C; (n-hexane); Yield: 15% (two steps). ee > 98%, $[\alpha]_D^{25} = -27.5$ (*c* 0.455, EtOH).

Ethyl (1*S*,2*S*,5*S*)-2-(*tert*-butoxycarbonylamino)-5-fluorocyclohex-3-enecarboxylate [(−)-10]

A white solid, mp 120-123 °C (n-hexane). Yield: 52%. ee > 98%, $[\alpha]_D^{25} = +39.1$ (*c* 0.405, EtOH).

Ethyl (1*S*,2*R*,3*R*)-2-(*tert*-butoxycarbonylamino)-3-fluorocyclohexanecarboxylate [(−)-12]

A white solid, mp 95–97 °C (n-hexane). Yield: 41%. ee > 98%, $[\alpha]_D^{25} = -7.1$ (*c* 0.35, EtOH).

General procedure for oxidation of 9 and 11

Sulfur trioxide-pyridine complex (3 equiv) and DMSO (2 mL) and Et_3N (4 equiv), were added at 0 °C to a solution of amino ester **9** or **11** (2 mmol) in CH_2Cl_2 (20 mL) and the mixture was stirred for 10 h at 20 °C. It was then diluted with CH_2Cl_2 (20 mL), washed with H_2O (3 × 20 mL), dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography on silica gel (n-hexane–EtOAc 3 : 1).

Ethyl (1*R,2*R**)-2-(*tert*-butoxycarbonylamino)-3-oxocyclohexanecarboxylate (15)**

A white solid, mp 60–63 °C; (n-hexane); Yield: 70%; (R_f 0.6, n-hexane–EtOAc 2 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, 3H, CH_3, J = 7.20 Hz), 1.43 (s, 9H, *t*Bu), 1.78–1.88 (m, 1H, CH_2), 1.97–2.22 (m, 3H, CH_2), 2.33–2.40 (1H, CH_2), 2.58–2.63 (m, 1H, CH_2), 3.78–3.82 (m, 1H, H-1), 4.13–4.18 (m, 2H, OCH_2), 4.30–4.36 (m, 1H, H-2), 5.62 (brs, 1H, N–H). Anal. Calcd. for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.61; H, 7.84; N, 4.62.

Ethyl (1*S,2*R**)-2-(*tert*-butoxycarbonylamino)-3-oxocyclohexanecarboxylate (16)**

A white solid, mp 90–92 °C; (n-hexane); Yield: 74%; (R_f 0.55, n-hexane–EtOAc 2 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, 3H, CH_3, J = 7.20 Hz), 1.41 (s, 9H, *t*Bu), 1.59–1.72 (m, 1H, CH_2), 2.07–2.20 (m, 3H, CH_2), 2.39–2.58 (m, 3H, CH_2 and H-1), 4.09–4.20 (m, 2H, OCH_2), 4.46–4.52 (m, 1H, H-2), 5.08 (brs, 1H, N–H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.5, 25.9, 28.4, 28.6, 41.1, 52.5, 60.6, 61.6, 80.2, 155.7, 172.2, 206.1. Anal. Calcd. for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.66; H, 7.88; N, 4.65.

General procedure for fluorination of keto-amino ester 15 or 16

Deoxofluor (50% in toluene) and 1 drop of EtOH were added at 0 °C to a solution of amino ester **15** or **16** (1 mmol) in CH_2Cl_2 (10 mL), and the mixture was stirred at this temperature for 8 h. Then the mixture was diluted with CH_2Cl_2 (20 mL) and washed with an aqueous solution of $NaHCO_3$. The organic layer was next dried over Na_2SO_4 and concentrated, and the crude product was purified by flash chromatography on silica gel (n-hexane–EtOAc 4 : 1).

Ethyl (1*R,2*R**)-2-(*tert*-butoxycarbonylamino)-3,3-difluorocyclohexanecarboxylate (17)**

A white solid, mp 83–85 °C (n-hexane). Yield: 32% (R_f 0.65, n-hexane–EtOAc 4 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, 3H, CH_3, J = 7.15 Hz), 1.41 (s, 9H, *t*Bu), 1.58–1.70 (m, 1H, CH_2), 2.04–2.20 (m, 3H, CH_2), 2.41–2.59 (m, 3H, CH_2 and H-1), 4.07–4.20 (m, 2H, OCH_2), 4.44–4.53 (m, 1H, H-2), 5.09 (brs, 1H, N–H). Anal. Calcd. for $C_{14}H_{23}F_2NO_4$: C, 54.71; H, 7.54; N, 4.56. Found: C, 54.43; H, 7.29; N, 4.27.

Ethyl (1*S,2*R**)-2-(*tert*-butoxycarbonylamino)-3,3-difluorocyclohexanecarboxylate (18)**

A white solid, mp 88-90 °C (n-hexane). Yield: 39% (R_f 0.60, n-hexane–EtOAc 4 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, 3H, CH_3, J = 7.15 Hz), δ = 1.40 (s, 9H, *t*Bu), 1.46–1.73 (m, 3H, CH_2), 1.78–1.84 (m, 1H, CH_2), 1.93–2.00 (m, 1H, CH_2), 2.17–2.23 (m, 1H, CH_2), 2.41–2.50 (m, 1H, H-1), 4.09–4.21 (m, 3H, OCH_2 and H-2), 4.71 (brs, 1H, N–H). Anal. Calcd. for $C_{14}H_{23}F_2NO_4$: C, 54.71; H, 7.54; N, 4.56. Found: C, 54.46; H, 7.20; N, 4.23.

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