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Fluorine-containing functionalized cyclopentene scaffolds through ring contraction and deoxofluorination of various substituted cyclohexenes

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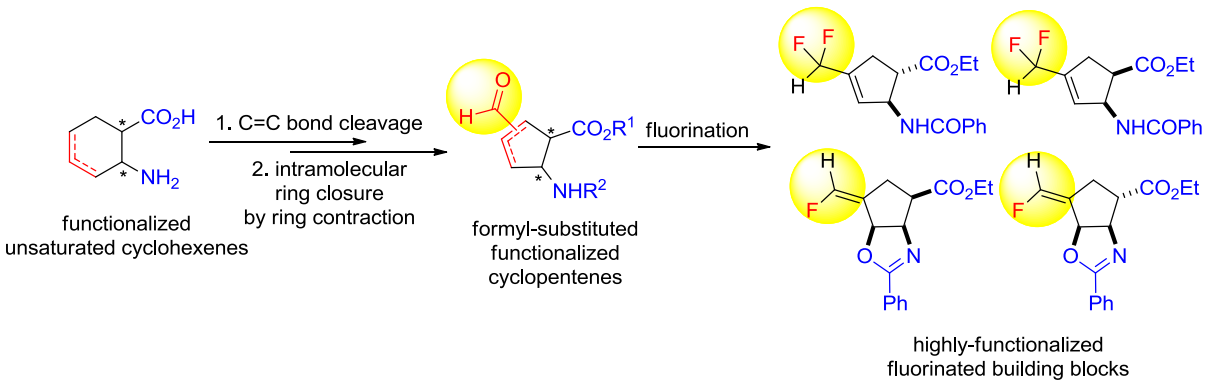
Abstract: Fluorination of some highly-functionalized cyclopentene derivatives, obtained from various substituted cyclohexenes through a ring-opening/ring-contraction procedure has been investigated. Transformations have been found to be highly substrate dependent resulting in various functionalized alicycles or heterocycles possessing allyl difluoride or vinyl fluoride moieties in their structure.

Graphical abstract:



Keywords: fluorine, ring contraction, aldol reaction, stereoselectivity, amino acids

Introduction

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Late-stage fluorination with various commercial nucleophilic reagents is a common method for the introduction of fluorine into an organic molecule and to access a number of different fluorine-containing molecular entities.[1] Late-stage fluorination based on hydroxy–fluorine or carbonyl–difluorine exchange is considered to be a relatively simple synthetic approach. In certain circumstances, these type of transformations were found to be highly substrate-dependent and the presence of various functional groups strongly determined and directed the outcome of the deoxofluorination reaction. Some deoxofluorinations proceed with high chemoselectivity; nucleophilic fluorinating agents, such as Deoxofluor, DAST or XtalFluor, are able to transform the hydroxy or oxo moieties of various highly-functionalized substrates with chemodiscrimination between these groups. Besides the expected products, however, it might often produce some surprising fluorinated or non-fluorinated scaffolds, in particular, in the case of compounds possessing multiple functional groups and stereogenic centers.[1-2] In view of the high pharmaceutical relevance of fluorinated organic molecules,[3] fluorination techniques including the late-stage fluorination protocol, such as oxo–difluorine interconversion, especially of highly functionalized scaffolds, are still considered to be an interesting challenge for synthetic chemists. Therefore, in order to investigate the chemical behavior under deoxofluorination conditions of some polyfunctionalized substrates, we selected some functionalized alicycles possessing carboxylate and amide or carbamate groups. The use of β-amino acid derivatives (as promising bioactive derivatives)[4] as well as some alicyclic esters and *N*-protected compounds allowed us to study both the independent and synergic habit of these moieties.

Results and Discussion

Taking into consideration some unexpected findings during our earlier experimental investigations on the late-stage fluorination of various functionalized alicycles,[2] our intention in the framework of this project was to continue and explore the chemical behavior of some variously polysubstituted six-membered carbocycles through oxidative ring-opening/ring-contraction/fluorination. Because of the high biological relevance of β-amino acids,[4] we have first selected some cyclohexene β-amino acid stereo- and regioisomers, as model compounds for our experiments. Thus, *cis*- or *trans*-2-aminocyclohexenecarboxylic acids **(±)-1** and **(±)-5** were first converted by known procedures to the corresponding dihydroxylated amino esters **(±)-2** and **(±)-6** (Scheme 1).[5]

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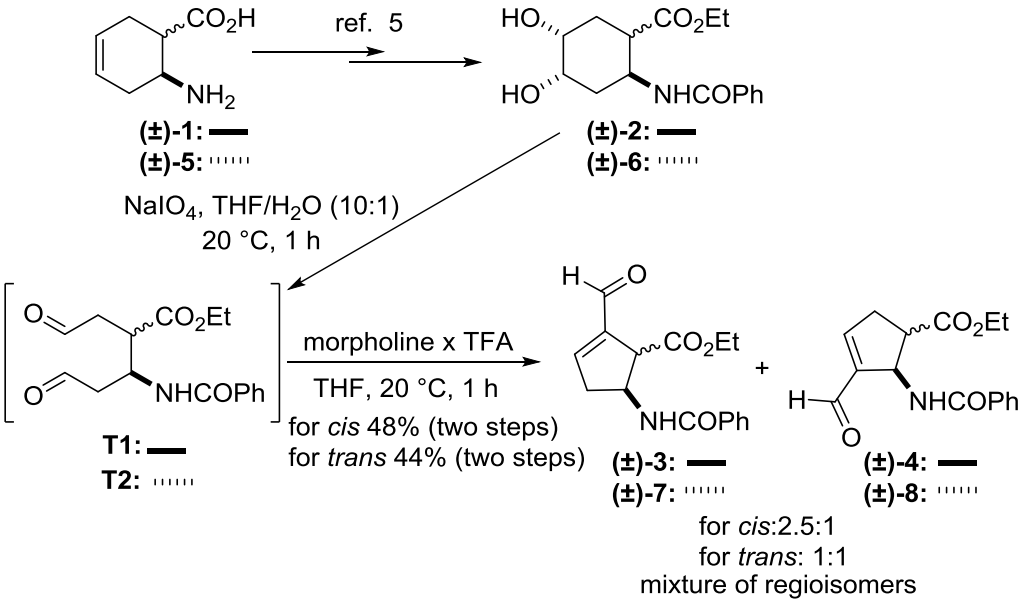

Scheme 1.

The aldol reaction and its intramolecular asymmetric version[6] of various substituted scaffolds (e.g. amino, nitro, halogen, hydroxy and other substituted compounds as well as carbonyl derivatives, or some oxo esters) are well-known basic approaches for the formation of varied molecules with an α,β-unsaturated carbonyl moiety.

Six-membered diol derivatives **(±)-2** and **(±)-6** were submitted to oxidative ring opening with $NaIO_4$ followed by intramolecular aldol reaction in the presence of morpholinium trifluoroacetate (TFA). These transformations gave the corresponding five-membered aldol regioisomers **(±)-3** and **(±)-4** (for the *cis* derivative) and **(±)-7** and **(±)-8** (for the *trans* isomer) in a non-selective manner as a mixture of a 2:1 and 1:1 ratio, respectively. These five-membered formyl-substituted β-amino esters might be considered to be valuable scaffolds for organic transformations, For example, the five-membered amino acids cispentacin and icofungipen are known as antibacterial agents.[4a]

Unfortunately, all our attempts to separate the formyl-substituted cyclopentene amino ester regioisomers shown in Scheme 1 failed. This failure, however, did not discourage us to continue our investigation using *cis*-2-aminocyclohex-3-ene carboxylic acid **(±)-9** an isomer of **(±)-1** and **(±)-5**. Compound **(±)-9** was converted to the corresponding diol derivative **(±)-10** applying a literature procedure.[5] Vicinal diol **(±)-10**, in turn, was subjected to the $NaIO_4$-mediated oxidative ring opening, followed by intramolecular ring closure induced by the morpholine salt. Contrary to our results presented in Scheme 1, cyclization of the unstable

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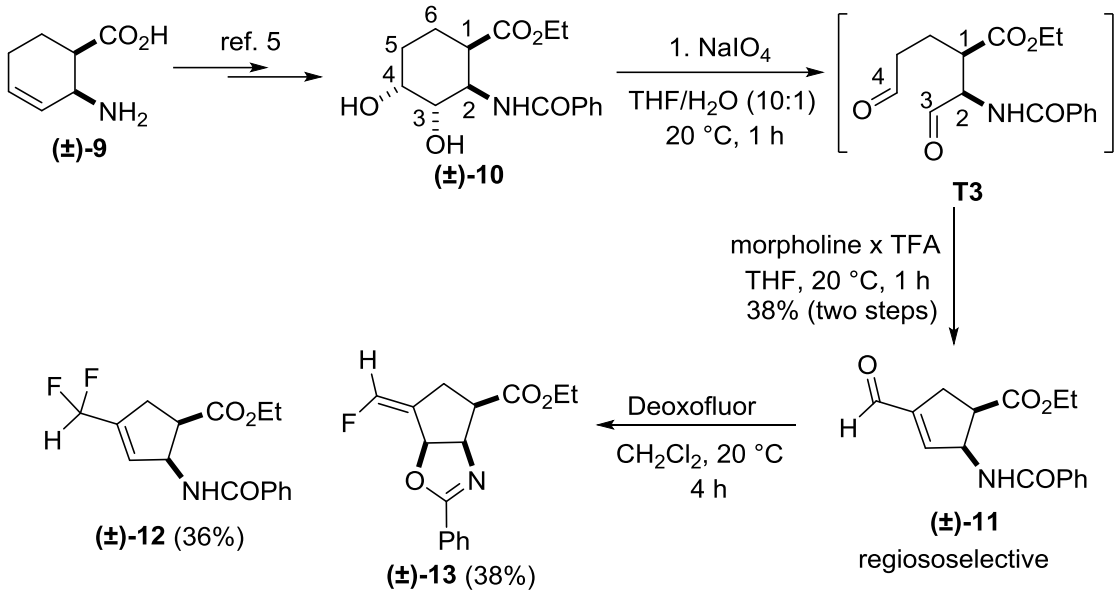
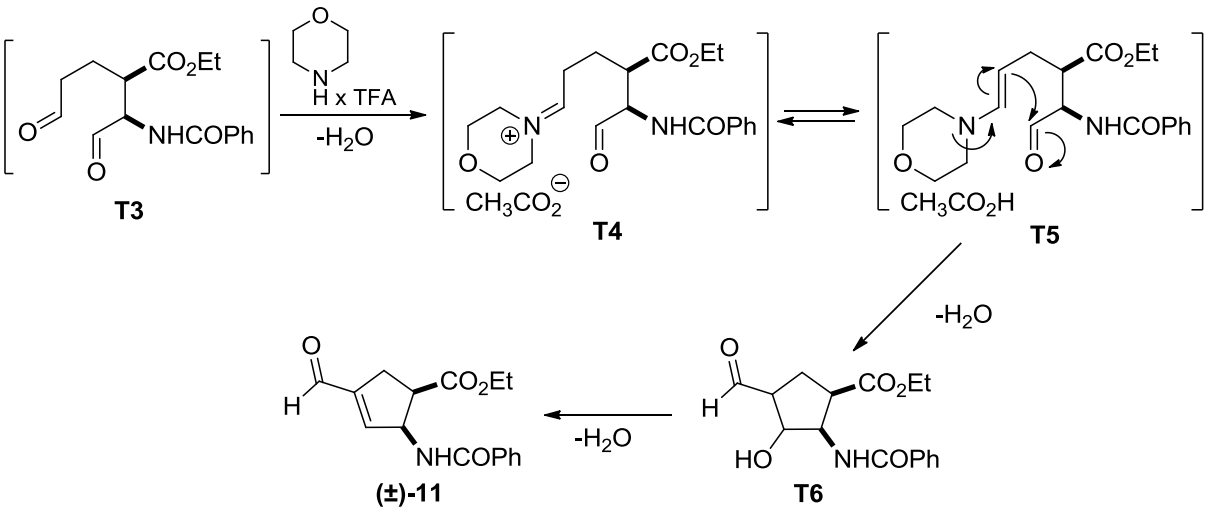
diformyl derivative **T3** proceeded with full selectivity furnishing unsaturated aldehyde derivative **(±)-11** as the single product (Scheme 2).



Scheme 2.

The cyclization process to **(±)-11** can be interpreted as shown in Scheme 3. Intramolecular hydrogen bonding effects in the transition state are probably responsible for the selectivity of the reaction. A stable structure may arise through a hydrogen bonding interaction between the amide NH and enamine nitrogen lone electron pair (formed in the reaction of morpholine with the formyl group located furthest from the amide). On the other hand, an enamine intermediate resulting from the reaction of morpholine with the formyl moiety close to the amide would afford an unfavorable structure (Figure 1).



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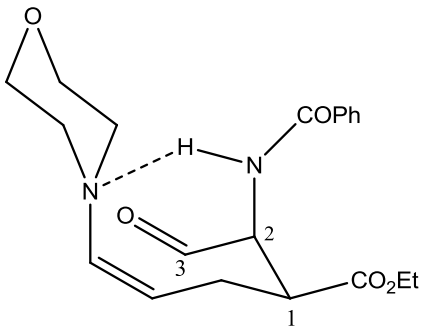
Scheme 3.



T5

Figure 1.

In continuation, cyclopentene acylamino ester **(±)-11** possessing an α,β-unsatursated aldehyde moiety with two electrophilic centers for 1,2- or 1,4-addition was subjected to fluorination under various experimental conditions, affording practically the same result. The experiments were systematically performed under various conditions in view of the used solvents (CH_2Cl_2, PhMe, THF), nucleophilic fluorinating agents (Deoxofluor, DAST), and temperature (0 °C, room temperature). Unfortunately, no significant effect either on the yield or selectivity of the products could be found. Namely, two products were formed nearly in 1:1 ratio, which could be separated by chromatography, isolated and characterized by NMR or X-ray analysis. One of the products was identified as the expected difluorinated compound **(±)-12** (Figure 2 and Scheme 2). The other product, **(±)-13**, somewhat surprisingly, was identified as a heterocyclic compound with a vinyl fluoride moiety. While the formation of product **(±)-12** with an allyl difluoride element is unambiguous, formation of **(±)-13** might be the result of an intramolecular attack of the amide oxygen atom to the electrophilic sp^2 carbon atom of intermediate **T7**. It contains a good leaving group system formed from the formyl group and Deoxofluor leading *Z*-selectively to an oxazoline derivative with a vinyl fluoride moiety (Scheme 4). The structure of **(±)-13** was determined on the basis of 2D NMR analysis.

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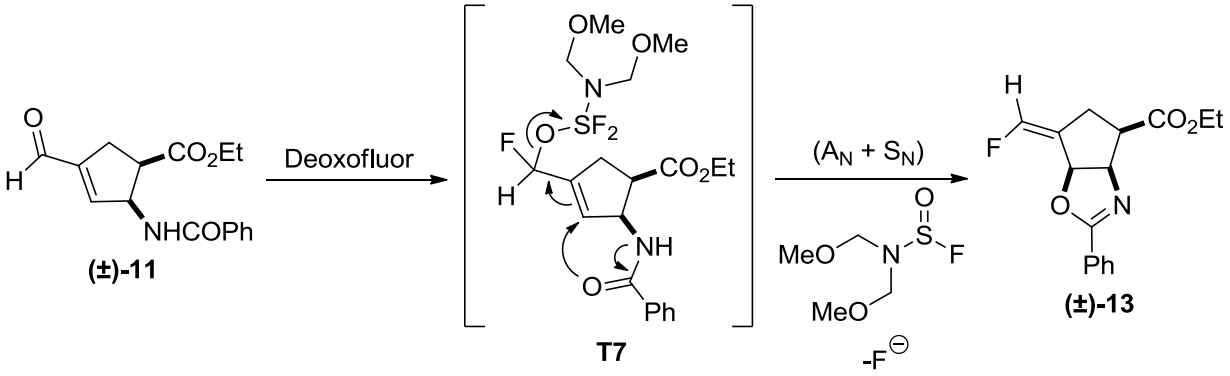

Scheme 4.

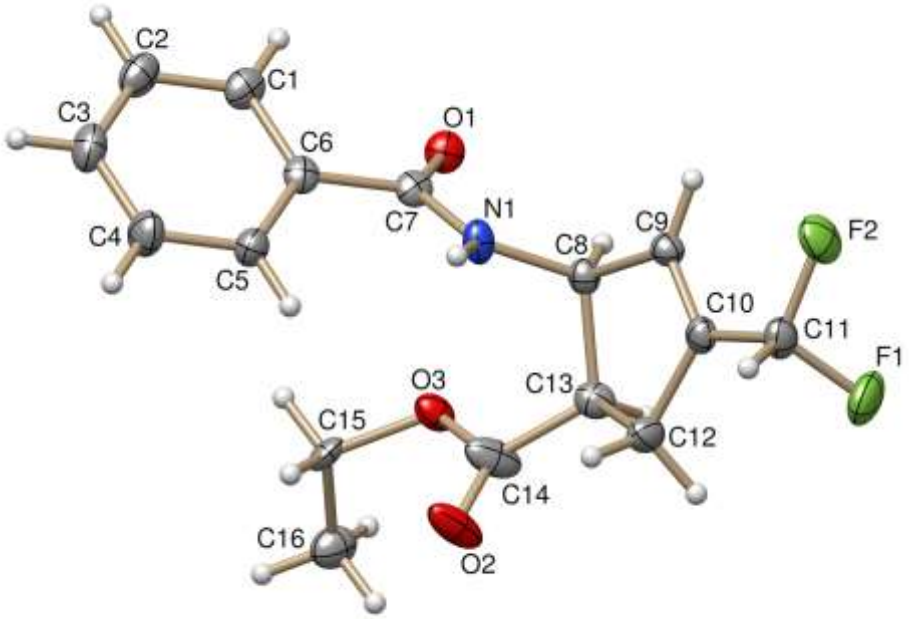

Figure 2. X-ray structure of **(±)-12**.

Fluorovinylation as well as the resulting fluorovinyl compounds as important elements in many biologically relevant compounds have received special attention in synthetic organic and pharmaceutical chemistry.[7-8a] In addition, allyl difluorides are motifs found in a series of pharmaceuticals and agrochemicals.[8] In view of the importance of these fluorinated derivatives, we found it interesting to continue our investigation of the intramolecular cyclization and subsequent fluorination protocol using other scaffolds. Diol derivative **(±)-14**, a stereoisomer of **(±)-10** accessed from **(±)-9**, underwent ring opening in reaction with $NaIO_4$ giving formyl-substituted cyclic amino ester **(±)-15** through unstable dialdehyde derivative

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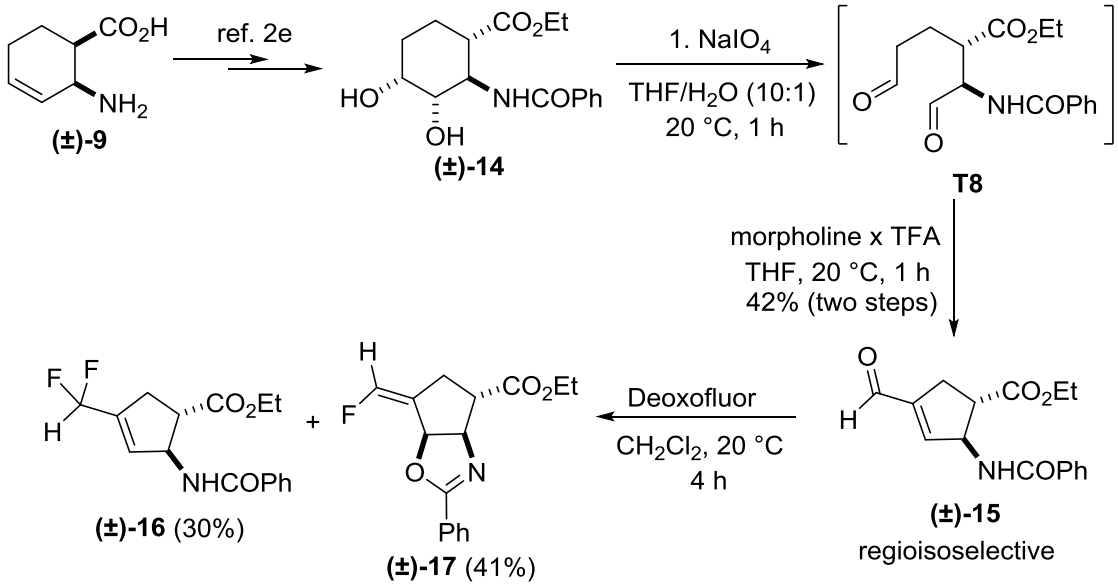
(±)-T8 as a result of intramolecular condensation (Scheme 5). Compound **(±)-15** on treatment with Deoxofluor, analogously to its *cis* counterpart, provided products **(±)-17** and **(±)-16** in a nearly 1.3:1 ratio. These were separated by column chromatography and identified as difluorinated compound **(±)-16** (minor, Figure 3) and the cyclized major oxazoline compound **(±)-17**.



Scheme 5.

The experimental findings described above with respect to oxidative ring-opening/intramolecular aldol reaction/fluorination performed with some cyclic β-amino acid derivatives motivated us to continue these investigations on other six-membered systems as well. The selected compounds bearing either ester or protected amino groups on their skeleton allowed to test the independent influence of the functional groups on the outcome of the reaction.

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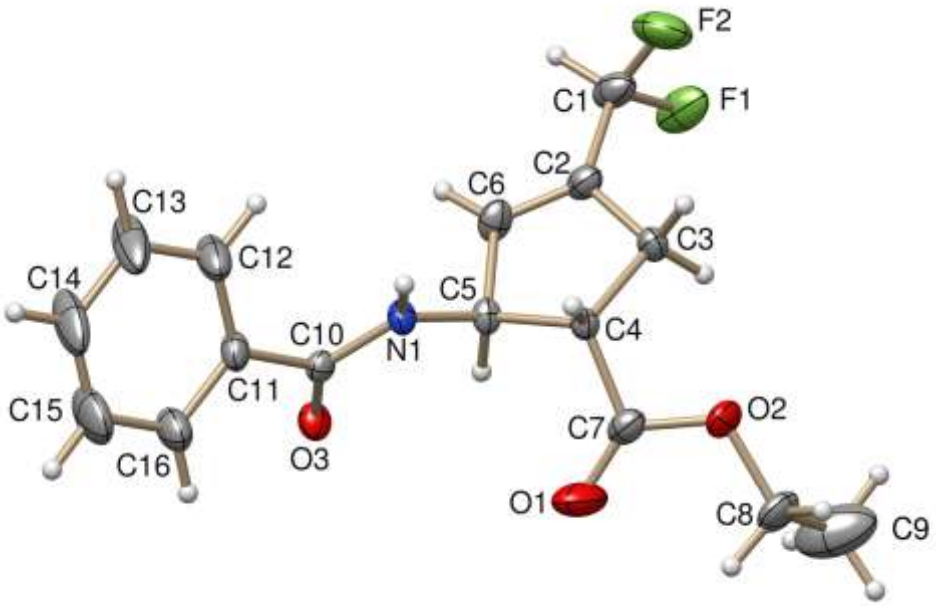
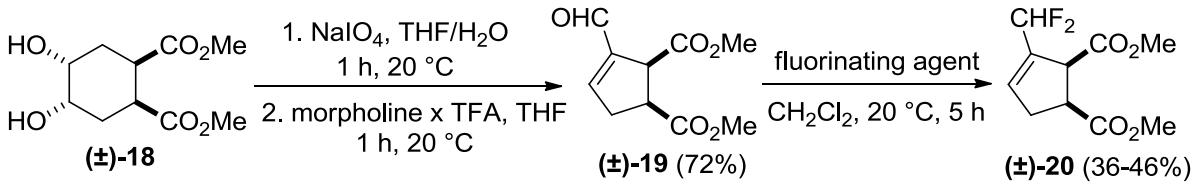


Figure 3. X-ray structure of **(±)-16**.

First we started with dihydroxylated diester **(±)-18**.[2e] This symmetric molecule gave formyl-substituted derivative **(±)-19** as the single product as a result of ring-opening/intramolecular cyclization. Fluorination of this diester with DAST or Deoxofluor under various experimental conditions furnished allyl difluoride derivative **(±)-20** as the sole product. The highest yield was attained with DAST in CH_2Cl_2 at room temperature (Scheme 6). The selective formation can be attributed to the absence of the internal nucleophile.



Scheme 6.

More interesting results have been expected by the evaluation of six-membered benzyl cyclohexenecarboxylate **(±)-21**.[9] Dihydroxylation of **(±)-21** provided an inseparable mixture of *cis* and *trans* diols **(±)-22**. Since both isomers give the same dialdehyde, this mixture was further used in the oxidative ring-opening/cyclization step. According to our expectation, the intramolecular aldol reaction afforded two formylated derivatives which, in turn, were separated and identified as compounds **(±)-23** (minor) and **(±)-24** (major). Fluorination of **(±)-**

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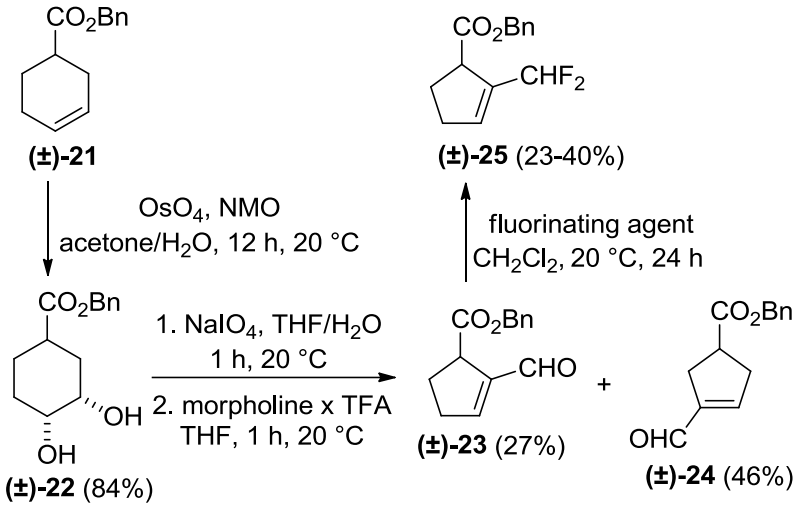
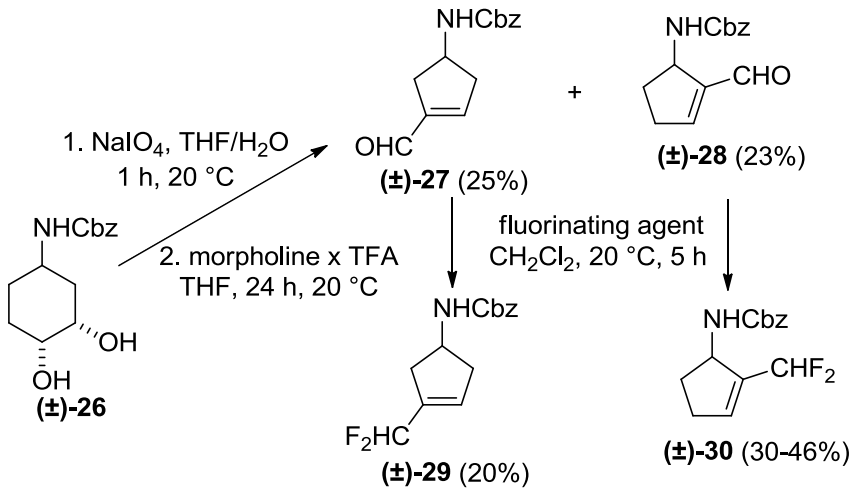
23 under various conditions with Deoxofluor in CH_2Cl_2 yielded a single product, the corresponding geminal difluorinated substance **(±)-25** (Scheme 7). Unfortunately, all attempts for fluorination of the major isomer **(±)-24**, under a number of experimental conditions, failed and only decomposed materials could be detected.



Scheme 7.

Next, we performed related experiments using amino-substituted cyclohexane derivative **(±)-26**.[10] Oxidative ring-opening/aldol cyclization of **(±)-26**, again, gave two products in approximately a 1:1 ratio.



Scheme 8.

Compounds **(±)-27** and **(±)-28** could be separated and characterized. Interestingly, when these were subjected to fluorination, no intramolecular ring closure with the internal assistance of the carbamate was observed contrary to the reaction of **(±)-11** or **(±)-15**. Instead,

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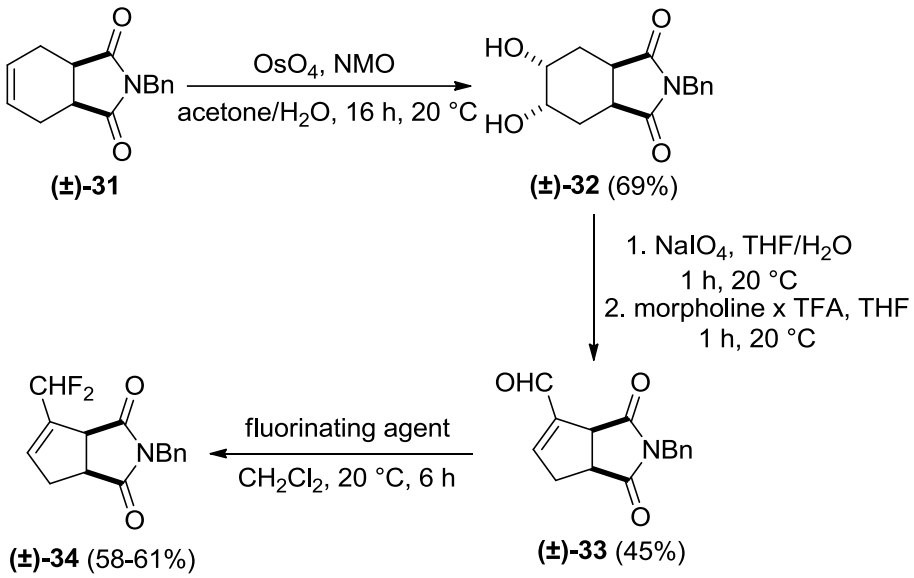
only geminal difluorinated products **(±)-29** and **(±)-30** were detected and isolated. The highest yields, again, were attained with the use of DAST in CH_2Cl_2 at room temperature (Scheme 8).Noteworthy, that substituted five-membered ring systems, in general, are more expensive than their six-membered analogs. Consequently, functionalized cyclopentene derivatives synthesized according to Schemes 6–8 might be regarded as valuable scaffolds for a wide variety of further transformations.

Finally, the behavior of a bicyclic system was also investigated. Dihydroxylation of imide **(±)-31** proceeded *cis*-selectively and resulted in diol **(±)-32**. Being a symmetric derivative, its ring-opening/cyclization reactions provided compound **(±)-33** as the single formyl-substituted product. This, in turn, gave under fluorination a single compound [**(±)-34**] with the highest yield attained with DAST (Scheme 9).



Scheme 9.

Conclusions

The synthesis of various fluorine-containing molecular scaffolds has been achieved from readily available six-membered functionalized carbocycles involving oxidative ring-opening/ring-contraction/fluorination sequences leading to molecules possessing allyl or vinyl fluoride moieties. Ring closing through intramolecular aldol reaction has been found to be substrate dependent and afforded various functionalized α,β-unsaturated aldehyde systems, whose fluorination gave either 1,2- or 1,4-addition products. The extension of these methods towards the access of the enantiomers, as well as studies on the regioselectivity of the intramolecular aldol reaction on various systems are currently being studied in our laboratory.

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Furthermore, additional experiments are currently investigated in our group on related transformations with other nucleophilic reagents and on various other highly-functionalized cycloalkane substrates.

Acknowledgments

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Experimental section

General procedure for ring contraction reactions. Synthesis of formyl-substituted cyclopentene amino esters:

To a solution of diol derivative (200 mg, 0.65 mmol) in THF/H_2O (11 mL, v/v 10:1) $NaIO_4$ (279 mg, 1.3 mmol) was added and the reaction mixture was stirred for 1 h at room temperature under an Ar atmosphere, resulting in the corresponding diformyl derivative. Water (20 mL) was then added to the reaction mixture and it was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phases were dried over Na_2SO_4, filtered and evaporated *in vacuo*. The resulting unstable dialdehyde was dissolved in 10 ml of dry THF followed by the addition of morpholinium TFA salt (131 mg, 0.65 mmol) . The mixture was stirred for 1 h at room temperature, then washed with water (2 × 15 ml), dried over Na_2SO_4, filtered and evaporated under reduced pressure. Purification of the crude mixture by means of column chromatography on silica gel (*n*-hexane-EtOAc) yielded the corresponding α,β-unsaturated aldehyde derivative.

General procedure for the fluorination of formyl-substituted cyclopentene amino esters:

To a solution of formyl derivative (144 mg, 0.5 mmole) in CH_2Cl_2 (10 mL) DAST or Deoxofluor (see text) was added at 20 °C and the mixture was stirred at this temperature for 4 h. Then it was diluted with CH_2Cl_2 (20 mL), washed with saturated $NaHCO_3$ solution (2 × 15 mL), dried (Na_2SO_4) and concentrated and the crude residue was purified by column chromatography on silica gel.

General procedure for dihydroxylation:

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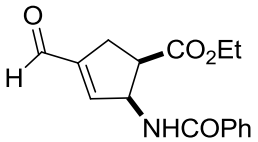
To a stirred solution of substituted cycloalkene (10 mmol) in acetone (30 ml) and water (3 ml), OsO_4 (2% in *t*-BuOH, 0.3 mL), and NMO (1.2 equiv) were added and the resulting mixture was stirred at r.t. for the time given in the text. Upon completion of the reaction, the mixture was treated with saturated aqueous Na_2SO_3 solution and then extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc or *n*-hexane/acetone).

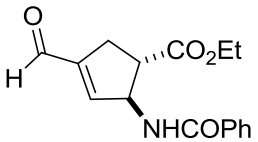
Characterization of the synthesized substances

Ethyl (1*R,2*S**)-2-benzamido-4-formylcyclopent-3-enecarboxylate, (±)-11**



White solid; yield: 38% (two steps); mp 85-88 °C; R_f = 0.40, *n*-hexane/EtOAc 1:2; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.24 (t, 3H, CH_3, J = 7.12 Hz), 2.85-3.10 (m, 2H, CH_2), 3.57-3.68 (m, 1H, H-1), 4.08-4.24 (m, 2H, OCH_2), 5.77-5.87 (m, 1H, H-2), 6.74-6.81 (m, 1H, H-3), 7.12 (brs, 1H, N-H), 7.42-7.60 (m, 3H, Ar-H), 7.75-7.84 (m, 2H, Ar-H), 9.87 (s, 1H, C*H*O); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 14.1, 31.9, 45.3, 55.8, 61.4, 127.0, 128.6, 132.0, 133.6, 146.4, 147.8, 166.6, 173.2, 189.1; Anal. Calcd for $C_{16}H_{17}NO_4$: C 66.89, H 5.96, N 4.88; found: C 66.58, H 5.60, N 4.57.

Ethyl (1*S,2*S**)-2-benzamido-4-formylcyclopent-3-enecarboxylate, (±)-15**



White solid; yield: 42% (two steps); mp 141-143 °C; R_f = 0.36, *n*-hexane/EtOAc 1:2; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.26 (t, 3H, CH_3, J = 7.14 Hz), 2.73-2.84 (m, 1H, CH_2), 2.98-3.08 (m, 1H, CH_2), 3.15-3.26 (m, 1H, H-1), 4.15-4.25 (m, 2H, OCH_2), 5.48-5.57 (m, 1H, H-2), 6.60 (brs, 1H, N-H), 6.74-6.80 (m, 1H, H-3), 7.39-7.57 (m, 3H, Ar-H), 7.74-7.83 (m, 2H, Ar-H), 9.79 (s, 1H, C*H*O); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 14.5, 31.8, 50.2, 60.2, 61.8, 127.4, 129.1, 132.4, 134.1, 145.7, 148.6, 167.7, 173.5, 189.4; Anal. Calcd for $C_{16}H_{17}NO_4$: C 66.89, H 5.96, N 4.88; found: C 67.19, H 5.62, N 4.55.

Ethyl (1*R,2*S**)-2-benzamido-4-(difluoromethyl)cyclopent-3-enecarboxylate, (±)-12**

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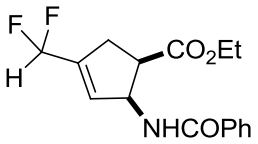
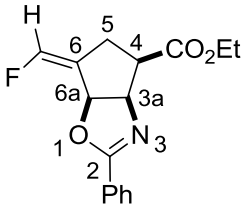


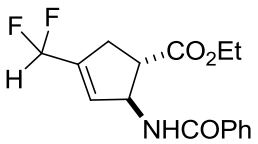
White solid; yield: 36%; mp 85-86 °C; R_f = 0.50, *n*-hexane/EtOAc 2:1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.18 (t, 3H, CH_3, J = 7.14 Hz), 2.71-2.82 (m, 1H, CH_2), 2.95-3.07 (m, 1H, CH_2), 3.55-3.65 (m, 1H, H-1), 4.02-4.18 (m, 2H, OCH_2), 5.61-5.72 (m, 1H, H-2), 6.00-6.07 (m, 1H, H-3), 6.10-6.43 (t, 1H, J = 55.3 Hz, C*H*F_2), 6.70 (brs, 1H, N-H), 7.38-7.54 (m, 3H, Ar-H), 7.69-7.78 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 14.1, 32.0, 45.6, 55.5, 61.3, 110.1 and 112.0 and 113.8 (^1J = 235.3 Hz), 127.0, 128.7, 131.6 and 131.7 and 131.8 (^3J = 8.7 Hz), 131.8, 133.9, 139.8 and 140.2 and 140.2 (^2J = 23.8 Hz), 166.6, 172.9; ^{19}F NMR (100 MHz, $CDCl_3$): δ = -116.7 (d, $^2J_{HF}$ = 54.8 Hz), -116.8 (d, $^2J_{HF}$ = 55.1 Hz); MS: (ESI, pos) m/z = 310 (M + 1); Anal. Calcd for $C_{16}H_{17}F_2NO_3$: C 62.13, H 5.54, N 4.53; found: C 62.49, H 5.20, N 4.18.

Ethyl (3a*R,4*R**,6a*S**,*Z*)-6-(fluoromethylene)-2-phenyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]oxazole-4-carboxylate, (±)-13**



White solid; yield: 38%; mp 60-62 °C; R_f = 0.55, *n*-hexane/EtOAc 2:1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.37 (t, 3H, CH_3, J = 7.12 Hz), 2.49-2.64 (m, 1H, CH_2), 2.79-2.90 (m, 1H, CH_2), 3.06-3.18 (m, 1H, H-4), 4.25-4.37 (m, 2H, OCH_2), 5.04-5.13 (m, 1H, H-3a), 5.34-5.42 (m, 1H, H-6a), 6.78-7.05 (dd, 1 H, *H*CF, J = 82.05 Hz, J = 2.54 Hz), 7.36-7.54 (m, 3H, Ar-H), 7.87-7.98 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 14.7, 25.5, 49.5, 61.2, 73.5, 82.4 and 82.5 (^3J = 11.4 Hz), 123.1 and 123.2 (^2J = 8.8 Hz), 127.5, 128.7, 129.0, 132.0, 146.4 and 149.0 (^1J = 262.7 Hz), 164.9, 170.9; ^{19}F NMR (100 MHz, $CDCl_3$): δ = -124.4 (d, ^2J = 82.0 Hz); MS: (ESI, pos) m/z = 291 (M + 1); Anal. Calcd for $C_{16}H_{16}FNO_3$: C 66.43, H 5.57, N 4.84; found: C 66.09, H 5.21, N 5.19.

Ethyl (1*S,2*S**)-2-benzamido-4-(difluoromethyl)cyclopent-3-enecarboxylate, (±)-16**



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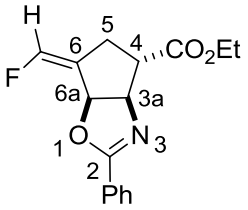
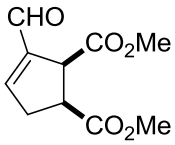
White solid; yield: 30%; mp 83-85 °C; R_f = 0.45, *n*-hexane/EtOAc 2:1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.27 (t, 3H, CH_3, J = 7.12 Hz), 2.77-2.99 (m, 2H, CH_2), 3.05-3.15 (m, 1H, H-1), 4.12-4.27 (m, 2H, OCH_2), 5.45-5.55 (m, 1H, H-2), 6.02-6.09 (m, 1H, H-3), 6.09-6.41 (t, 1H, C*H*F_2, J = 55.36 Hz, and brs, 1H, N-H), 7.39-7.57 (m, 3H, Ar-H), 7.71-7.82 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 14.1, 32.0, 50.3, 59.4, 61.3, 110.0 and 111.9 and 113.8 (^1J = 235.2 Hz), 127.0, 128.7, 131.8, 132.0 and 132.1 and 132.2 (^3J = 8.9 Hz), 133.9, 138.7 and 138.9 and 139.0 (^2J = 23.8 Hz), 167.0, 173.1; ^{19}F NMR (100 MHz, $CDCl_3$): δ = -116.7 (d, $^2J_{HF}$ = 54.8 Hz), -116.9 (d, $^2J_{HF}$ = 55.6 Hz); MS: (ESI, pos) m/z = 310 (M + 1); Anal. Calcd for $C_{16}H_{17}F_2NO_3$: C 62.13, H 5.54, N 4.53; found: C 61.81, H 5.19, N 4.19.

Ethyl (3a*R,4*S**,6a*S**,*Z*)-6-(fluoromethylene)-2-phenyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]oxazole-4-carboxylate, (±)-17**



Yellow oil; yield: 41%; R_f = 0.50, *n*-hexane/EtOAc 2:1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.27 (t, 3H, CH_3, J = 7.12 Hz), 2.47-2.60 (m, 1H, CH_2), 2.87-2.97 (m, 1H, CH_2), 3.21-3.30 (m, 1H, H-4), 4.12-4.23 (m, 2H, OCH_2), 5.01-5.09 (m, 1H, H-3a), 5.40-5.47 (m, 1H, H-6a), 6.78-7.05 (d, 1 H, *H*CF, J = 82.03 Hz), 7.36-7.53 (m, 3H, Ar-H), 7.88-7.96 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 14.5, 27.9, 50.5, 61.5, 74.7, 82.9 and 83.1 (^3J = 10.9 Hz), 123.0 and 123.1 (^2J = 9.0 Hz), 127.5, 128.8, 128.8. 132.1, 146.8 and 149.4 (J = 262.6 Hz), 164.8, 173.8; ^{19}F NMR (100 MHz, $CDCl_3$): δ = -124.1 (d, $^2J_{HF}$ = 82.1 Hz); MS: (ESI, pos) m/z = 291 (M + 1); Anal. Calcd for $C_{16}H_{16}FNO_3$: C 66.43, H 5.57, N 4.84; found: C 66.80, H 5.23, N 4.50.

(1*S,2*S**)-Dimethyl 3-formylcyclopent-3-ene-1,2-dicarboxylate, (±)-19**



Pale yellow solid; yield 72%; mp 30-32 °C; R_f = 0.46, *n*-hexane/EtOAc 1:1; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 2.89 (ddd, 1H, ^2J = 19.20 Hz, ^3J = 8.90 Hz, ^3J = 2.95 Hz, H-5), 3.26 (ddt, 1H, ^2J = 19.20 Hz, ^3J = 8.85 Hz, ^3J = 2.25 Hz, H-5), 3.52 (q, 1H, J = 9.03 Hz, H-1), 3.68 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 4.07-4.12 (m, 1H, H-2), 7.02-7.06 (m, 1H, H-4), 9.71 (s, 1H,

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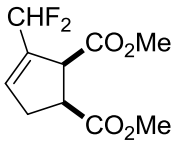
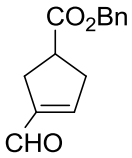
CHO); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 35.6, 46.5, 49.2, 52.2, 52.3, 144.2, 152.9, 171.7, 172.0, 187.7; MS (ESI, pos) m/z = 213 (M+1); Anal. Calcd for $C_{10}H_{12}O_5$: C 56.60, H 5.70; found: C 56.94, H 5.97.

(1*S,2*S**)-Dimethyl 3-(difluoromethyl)cyclopent-3-ene-1,2-dicarboxylate, (±)-20**



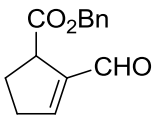
Pale yellow oil; yield 46%; R_f = 0.43, *n*-hexane/EtOAc 3:1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.64-2.78 (m, 1H, H-5), 2.99-3.13 (m, 1H, H-5), 3.49 (q, J = 8.99 Hz, 1H, H-2), 3.69 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.90-3.96 (m, 1H, H-1), 6.09-6.41 (t, J = 55.44 Hz, 1H, CHF_2), 6.27-6.32 (m, 1H, H-4); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 34.2, 46.9, 50.0 and 50.0 (^3J = 1.27 Hz), 52.1, 52.3, 110.1 and 112.0 and 113.9 (^1J = 235.58 Hz), 135.0 and 135.2 and 135.4 (^2J = 23.27 Hz), 136.5 and 136.5 and 136.6 (^3J = 8.40 Hz), 172.0, 172.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -114.55 (dd, $^2J_{FF}$ = 302.57 Hz, $^2J_{HF}$ = 55.10 Hz), -117.93 (dd, $^2J_{FF}$ = 303.27 Hz, $^2J_{HF}$ = 55.72 Hz); Anal. Calcd for $C_{10}H_{12}F_2O_4$: C 51.28, H 5.16; found: C 50.98, H 4.78.

Benzyl 3-formylcyclopent-3-enecarboxylate, (±)-24



Pale yellow oil; yield 46%; R_f = 0.58, *n*-hexane/EtOAc 2:1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.78-3.08 (m, 4H, H-2 and H-5), 3.24-3.40 (m, 1H, H-1), 5.15 (s, 2H, benzylic CH_2), 6.74-6.80 (m, 1H, H-4), 7.30-7.41 (m, 5H, CH-Ar), 9.75 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 32.5, 36.9, 41.3, 66.7, 128.2, 128.4, 128.6, 135.7, 145.7, 149.9, 174.6, 189.1; MS (ESI, pos) m/z = 231 (M+1); Anal. Calcd for $C_{14}H_{14}O_3$: C 73.03, H 6.13; found: C 72.75, H 5.77.

Benzyl 2-formylcyclopent-2-enecarboxylate, (±)-23



Pale yellow oil; yield 27%; R_f = 0.49, *n*-hexane/EtOAc 2:1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.11-2.23 (m, 1H, H-5), 2.30-2.43 (m, 1H, H-5), 2.56-2.69 (m, 1H, H-4), 2.70-2.83 (m, 1H,

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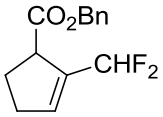
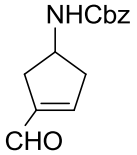
H-4), 3.78-3.87 (m, 1H, H-1), 5.14 (s, 2H, benzylic CH_2), 6.98-7.04 (m, 1H, H-3), 7.28-7.40 (m, 5H, CH-Ar), 9.77 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 28.6, 33.1, 47.1, 66.7, 128.1, 128.2, 128.5, 135.9, 145.5, 154.4, 173.7, 188.3; MS (ESI, pos) m/z = 253 (M+Na); Anal. Calcd for $C_{14}H_{14}O_3$: C 73.03, H 6.13; found: C 73.34, H 5.79.

Benzyl 2-(difluoromethyl)cyclopent-2-enecarboxylate, (±)-25



Pale yellow oil; yield 40%; R_f = 0.50, *n*-hexane/EtOAc 8:1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.20-2.37 (m, 2H, H-5), 2.39-2.52 (m, 1H, H-4), 2.54-2.69 (m, 1H, H-4), 3.70-3.79 (m, 1H, H-1), 5.09-5.19 (m, 2H, benzylic CH_2), 6.15-6.47 (t, J = 55.98 Hz, 1H, CHF_2), 6.24-6.30 (m, 1H, and H-3), 7.30-7.43 (m, 5H, CH-Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 28.3, 31.7, 48.4, 66.8, 110.2 and 112.5 and 114.8 (^1J = 235.89 Hz), 128.2, 128.3, 128.6, 135.7, 137.1 and 137.2 and 137.2 (^3J = 7.96 Hz), 173.6; MS (ESI, pos) m/z = 275 (M+Na); ^{19}F NMR ($CDCl_3$, 376 MHz) δ = -114.30 (dd, $^2J_{FF}$ = 298.98 Hz, $^2J_{HF}$ = 55.12 Hz), -117.64 (dd, $^2J_{FF}$ = 299.02 Hz, $^2J_{HF}$ = 55.99 Hz); Anal. Calcd for $C_{14}H_{14}F_2O_2$: C 66.66, H 5.59; found: C 66.99, H 5.95.

Benzyl (3-formylcyclopent-3-en-1-yl)carbamate, (±)-27



Pale yellow oil; yield 25%; R_f = 0.47, *n*-hexane/EtOAc 1:1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.37-2.48 (dd, J = 16.83 Hz, J = 2.70 Hz, 1H, H-5), 2.48-2.64 (d, J = 19.53 Hz, 1H, H-2), 2.87-2.99 (dd, J = 17.15 Hz, J = 7.82 Hz, 1H, H-5), 2.99-3.14 (dd, J = 19.21 Hz, J = 6.08 Hz, 1H, H-2), 4.36-4.57 (m, 1H, H-1), 4.84-5.01 (m, 1H, NH), 5.10 (s, 2H, benzylic CH_2), 6.76-6.86 (m, 1H, H-4), 7.28-7.47 (m, 5H, CH-Ar), 9.74 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 36.5, 41.8, 50.9, 67.2, 128.6, 128.7, 129.0, 136.7, 145.7, 149.9, 156.2, 189.7; MS (ESI, pos) m/z = 246 (M+1); Anal. Calcd for $C_{14}H_{15}NO_3$: C 68.56, H 6.16, N 5.71; found: C 68.88, H 6.45, N 5.38.

Benzyl (2-formylcyclopent-2-en-1-yl)carbamate, (±)-28

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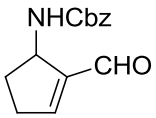
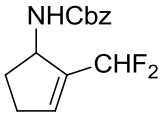


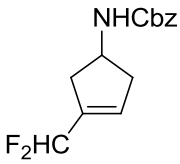
Pale yellow solid; yield 23%; mp 57-62 °C; R_f = 0.38, *n*-hexane/EtOAc 1:1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.87-2.05 (m, 1H, H-5), 2.41-2.63 (m, 2H, H-4 and H-5), 2.65-2.84 (m, 1H, H-4), 4.85-4.97 (m, 1H, H-1), 4.99-5.21 (m, 3H, benzylic CH_2 and NH), 6.99-7.10 (m, 1H, H-3), 7.24-7.45 (m, 5H, CH-Ar), 9.79 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 32.1, 32.6, 54.9, 67.1, 128.5, 128.9, 136.9, 145.7, 156.0, 156.3, 189.2; MS (ESI, pos) m/z = 246 (M+1); Anal. Calcd for $C_{14}H_{15}NO_3$: C 68.56, H 6.16, N 5.71; found: C 68.92, H 5.85, N 5.41.

Benzyl (2-(difluoromethyl)cyclopent-2-en-1-yl)carbamate, (±)-30



White solid; yield 46%; mp 48-53 °C; R_f = 0.64, *n*-hexane/EtOAc 2:1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 1.73-1.88 (m, 1H, H-5), 2.29-2.61 (m, 3H, H-4 and H-5), 4.78-5.01 (m, 2H, H-1 and NH), 5.04-5.23 (m, 2H, benzylic CH_2), 6.08-6.43 (t, J = 55.30 Hz, 1H, CHF_2), 6.27-6.33 (m, 1H, and H-3), 7.27-7.46 (m, 5H, CH-Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 30.5, 32.9, 56.0, 67.2, 110.5 and 112.9 and 115.2 (^1J = 235.41 Hz), 128.5, 128.5, 128.9, 136.9, 138.0 and 138.0 and 138.1 (^3J = 7.79 Hz), 156.1; ^{19}F NMR ($CDCl_3$, 376 MHz) δ = -113.07 (dd, $^2J_{FF}$ = 303.87 Hz, $^2J_{HF}$ = 55.61 Hz), -116.04 (dd, $^2J_{FF}$ = 303.23 Hz, $^2J_{HF}$ = 56.10 Hz); MS (ESI, pos) m/z = 268 (M+1); Anal. Calcd for $C_{14}H_{15}F_2NO_2$: C 62.91, H 5.66, N 5.24; found: C 63.20, H 5.31, N 5.51.

Benzyl (3-(difluoromethyl)cyclopent-3-en-1-yl)carbamate, (±)-29



Colorless oil; yield 20%; R_f = 0.39, *n*-hexane/acetone 4:1; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 2.27-2.40 (m, 2H, H-2 and H-5), 2.79-2.94 (m, 2H, H-2 and H-5), 4.40-4.51 (m, 1H, H-1), 4.90-5.03 (m, 1H, NH), 5.09 (s, 2H, benzylic CH_2), 5.96-6.04 (m, 1H, H-4), 6.04-6.36 (t, J=55.70 Hz, 1H, CHF_2), 7.28-7.41 (m, 5H, CH-Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 29.7, 36.9, 40.2, 50.5, 66.8, 110.7 and 112.6 and 114.5 (^1J = 235.57 Hz), 128.2, 128.2, 128.6, 131.4 and 131.5 and 131.6 (^3J = 9.13 Hz), 136.0 and 136.2 (^2J = 23.92 Hz), 136.4, 155.8; ^{19}F NMR

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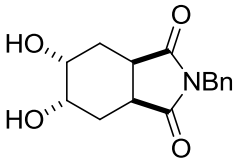
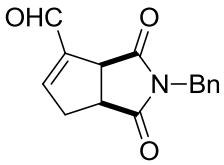
(CDCl$_3$, 471 MHz) δ = -115.48 (d, $^2J_{HF}$ = 55.77 Hz); MS (ESI, pos) m/z = 268 (M+1); Anal. Calcd for $C_{14}H_{15}F_2NO_2$: C 62.91, H 5.66, N 5.24; found: C 63.21, H 6.02, N 5.55.

(3a*R,5*R**,6*S**,7a*S**)-2-Benzyl-5,6-dihydroxyhexahydro-1H-isoindole-1,3(2H)-dione, (±)-32**



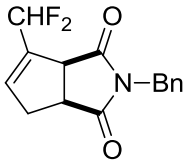
White solid; yield 69%; mp 135-138 °C; R_f = 0.29, *n*-hexane/acetone 1:1; ^{1}H NMR (D6-DMSO, 500 MHz) δ = 1.57-1.66 (m, 2H, H-4 and H-7), 1.86-1.96 (m, 2H, H-4 and H 7), 3.03-3.10 (m, 2H, H-3a and H-7a), 3.42-3.49 (m, 2H, H-5 and H-6), 4.52 (s, 2H, benzylic CH_2), 4.67 (d, J = 3.95 Hz, 2H, OH), 7.18-7.34 (m, 5H, CH-Ar); ^{13}C NMR (D6-DMSO, 125 MHz) δ = 27.4, 36.8, 40.5, 66.5, 126.7, 126.8, 127.9, 135.8, 178.7; MS (ESI, pos) m/z = 276 (M+1); Anal. Calcd for $C_{15}H_{17}NO_4$: C 65.44, H 6.22, N 5.09; found: C 65.79, H 6.48, N 5.34.

(3a*S,6a*S**)-2-Benzyl-1,3-dioxo-1,2,3,3a,6,6a-hexahydrocyclopenta[c]pyrrole-4-carbaldehyde, (±)-33**



Pale yellow solid; yield 45%; mp 115-132 °C; R_f = 0.38, *n*-hexane/acetone 3:2; ^{1}H NMR (D6-DMSO, 500 MHz) δ = 2.77-2.86 (m, 1H, H-6), δ = 3.02-3.12 (m, 1H, H-6), 3.67-3.75 (m, 1H, H-6a), 4.22-4.28 (m, 1H, H-3a), 4.51 (s, 2H, benzylic CH_2), 7.08-7.13 (m, 1H, H-5), 7.15-7.20 (m, 2H, CH-Ar), 7.22-7.34 (m, 3H, CH-Ar), 9.75 (s, 1H, CHO); 13C NMR (D6-DMSO, 125 MHz) δ = 36.1, 41.9, 43.5, 50.4, 127.7, 127.9, 129.0, 136.5, 142.0, 153.9, 175.7, 179.3, 188.7; MS (ESI, pos) m/z = 256 (M+1); Anal. Calcd for $C_{15}H_{13}NO_3$: C 70.58, H 5.13, N 5.49; found: C 70.94, H 4.86, N 5.16.

(3a*S,6a*S**)-2-Benzyl-4-(difluoromethyl)-6,6a-dihydrocyclopenta[c]pyrrole-1,3(2H,-3aH)-dione, (±)-34**



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White solid; yield 61%; mp 62-65 °C; R_f = 0.53, *n*-hexane/EtOAc 2:1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.81-3.03 (m, 2H, H-6), 3.49-3.64 (m, 1H, H-6a), 3.95-4.06 (m, 1H, H-3a), 4.57-4.70 (m, 2H, benzylic CH_2), 6.13-6.19 (m, 1H, H-5), 6.19-6.54 (t, J = 55.32 Hz, 1H, CHF_2), 7.24-7.38 (m, 5H, CH-Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 35.1, 42.5, 43.3, 51.5 and 51.5 (^3J = 3.46 Hz), 109.1 and 111.0 and 111.0 and 112.9 (^1J = 235.34 Hz, ^1J = 239.60 Hz), 128.1, 128.6, 128.7, 133.6 and 133.8 and 134.0 (^2J = 22.98 Hz), 134.2 and 134.3 and 134.3 (^3J = 7.06 Hz), 135.5, 175.5, 178.7; ^{19}F NMR ($CDCl_3$, 471 MHz) δ = -121.71 (dd, $^2J_{FF}$ = 299.62 Hz, $^2J_{HF}$ = 55.16 Hz), -113.29 (dd, $^2J_{FF}$ = 301.27 Hz, $^2J_{HF}$ = 56.43 Hz); MS (ESI, pos) m/z = 278 (M+1); Anal. Calcd for $C_{15}H_{13}F_2NO_2$: C 64.98, H 4.73, N 5.05; found: C 65.32, H 4.48, N 4.76.

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