Synthesis R. A. Ábrahámi et al. Feature

Functionalized Dialdehydes as Promising Scaffolds for Access to Heterocycles and β-Amino Acids: Synthesis of Fluorinated Piperidine and Azepane Derivatives

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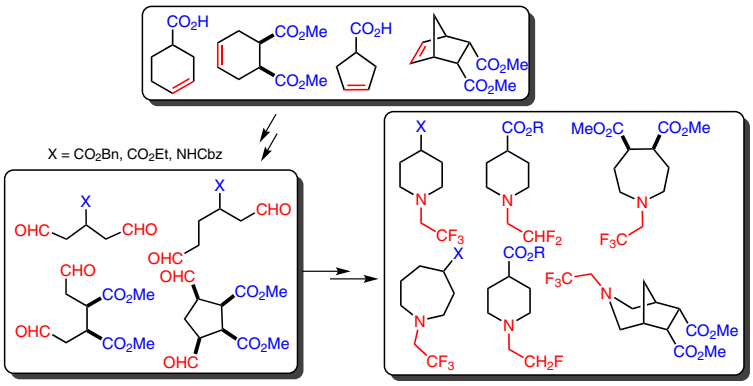

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Abstract Functionalized dialdehydes are considered important substrates that can be transformed into various substituted heterocyclic, alicyclic, and polysubstituted compounds. Here, we report a robust stereocontrolled procedure for the synthesis of novel functionalized trifluoromethyl-containing piperidine and azepane derivatives, based on oxidative ring cleavage of the C=C bond of diversely substituted cycloalkenes, followed by reductive ring closure of the diformyl intermediates in the presence of fluorine-containing amines.

Key Words aldehydes, alkylation, amino acids, bioorganic chemistry, heterocycles, piperidines, expansion

Introduction

Since the classical textbook example of tropinone synthesis, alicyclic and open-chain dialdehydes have been regarded as valuable scaffolds. They allow the construction of various saturated *N*-heterocyclic systems with different substituents and can serve as precursors that enable access to highly functionalized β-amino acid derivatives. Thus, the oxidative ring cleavage of unsaturated carbocyclic compounds followed by ring closure under reductive amination conditions serves as a methodology for the preparation of some heterocyclic systems (Figure 1), such as highly substituted piperidines, morpholine derivatives, and *N*-bridged bicyclic scaffolds.[1]

The oxidative ring cleavage of unsaturated, substituted mono- or bicyclic compounds, followed by transformations of the resulting diformyl intermediates as useful substrates, is an efficient and convenient tool for the synthesis of functionalized acyclic or monocyclic derivatives.[2]

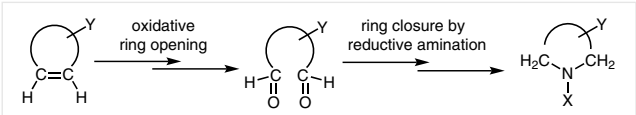
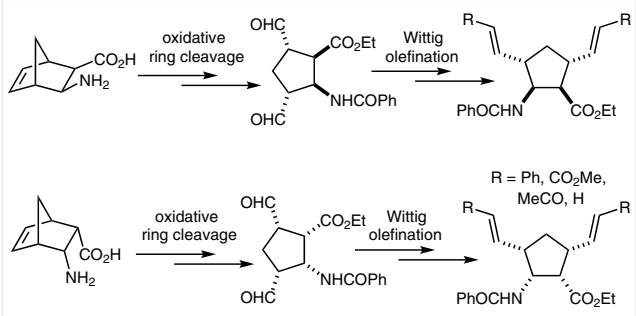


Figure 1 General scheme for the transformation of cycloalkenes into *N*-heterocycles via dialdehydes

Given the high chemical and biological relevance of β-amino acids,[3] during the last decade we have focused developing ways to access this type of compound. Based on these studies, our group has demonstrated that various carbocyclic and acyclic dialdehydes, derived from unsaturated mono- or bicyclic substances are useful intermediates for the synthesis of various functionalized β-amino derivatives.

A stereocontrolled transformation of unsaturated β-amino acids involving diformyl cyclopentanes is illustrated in Scheme 1. Carbocyclic dialdehydes, derived from norbornene β-amino acid stereoisomers by oxidative cleavage, were converted under Wittig reaction conditions into the corresponding alkenylated cyclopentane β-amino acid derivatives (Scheme 1).[4]



Scheme 1 Stereocontrolled synthesis of functionalized alkenylated cyclopentanes from disubstituted norbornenes via diformyl intermediates

The developed stereocontrolled method described above was efficiently extended to the synthesis of various functionalized open-chain β-amino acid derivatives. Starting from *cis*- or *trans*-cyclopentene β-amino acids, dialdehyde intermediates furnished the corresponding *anti*- and *syn*-dialkenylated acyclic derivatives with conservation of the configuration of the chiral centers (Scheme 2).[5]

By applying a similar strategy, the six-membered amino acid stereoisomers, after oxidative ring opening and Wittig olefination, provided novel functionalized open-chain β-amino acid derivatives.[6]

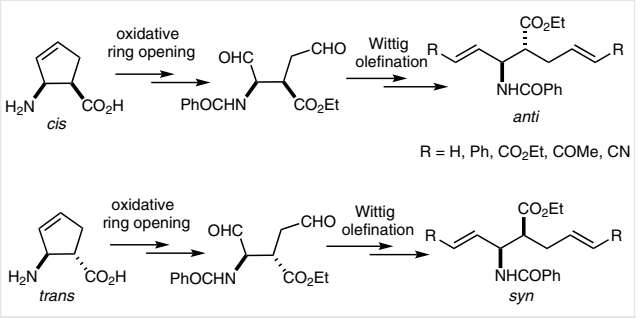
Biographical Sketches

Renáta A. Ábrahámi graduated as a pharmacist in 2015 from the University of Szeged (Hungary). She has been working at the Institute of Pharmaceutical Chemistry, University of Szeged since 2011. In 2015 she started her Ph.D. under the supervision of Loránd Kiss and Ferenc Fülöp. Her recent research topic focuses on the synthesis of variously functionalized six- or seven-membered *N*-heterocyclic derivatives and on the preparation of highly substituted fluorinated building elements.

Loránd Kiss completed his Ph.D. in 2002 in the Department of Organic Chemistry at Debrecen University (Debrecen, Hungary) under the supervision of Prof. Sándor Antus. In 2003, he joined the research group of Professor Ferenc Fülöp at the Institute of Pharmaceutical Chemistry, University of Szeged (Szeged, Hungary), where he started to work in the field of cyclic β-amino acid chemistry. He followed postdoctoral studies in the laboratories of Prof. Norbert De Kimpe at Ghent University (Ghent, Belgium), and Prof. Santos Fustero, at the Department of Organic Chemistry, University of Valencia (Valencia, Spain). He has published 72 scientific papers in reputed journals. He is currently a faculty member at the Institute of Pharmaceutical Chemistry, University of Szeged. His scientific interest is directed towards the selective functionalization cyclic β-amino acids and on the synthesis of highly functionalized fluorinated building blocks.

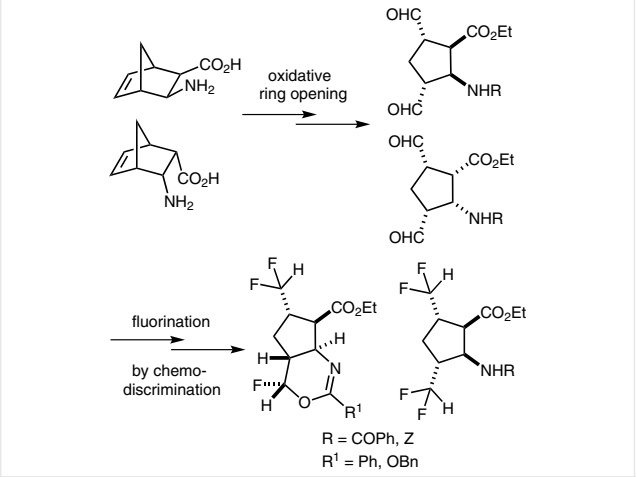
Santos Fustero was born in Aínsa, Spain, in 1949. He studied chemistry at the University of Zaragoza, where he obtained his B.Sc. degree in 1972. He received his Ph.D. in organic chemistry in 1975 from the same University, working in the field of heterocyclic chemistry under the supervision of Professor J. Barluenga and Professor V. Gotor. He spent two years as a postdoctoral research associate at Professor H. Lehmkuhl's laboratory at Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr, Germany, researching organometallic chemistry. In 1983, he became Associate Professor at the University of Oviedo, Spain, and, in 1990, he was promoted to Full Professor in Organic Chemistry at the University of Valencia. In 2005, he became research group leader at Centro de Investigación 'Príncipe Felipe' (CIPF) in Valencia. His research interests include organofluorine and medicinal chemistry, organocatalysis, and new reaction methodologies.

Ferenc Fülöp was born in Szank, Hungary in 1952. He received his MSc in Chemistry in 1975 and his Ph.D. in 1979 from József Attila University, Szeged, Hungary. At the beginning of his carrier he worked in Chinoin Pharmaceuticals, Budapest for six years. In 1991, he was appointed as a full professor at the Institute of Pharmaceutical Chemistry, University of Szeged, and since 1998 has been the head of the Institute. He is a member of the Hungarian Academy of Sciences and has a wide range of research interests in synthetic organic chemistry. His recent activities have focused on the use of amino alcohols and β-amino acids in enzymatic transformations, asymmetric syntheses, foldamer construction, and flow chemistry, in view of the development of pharmacologically active compounds.



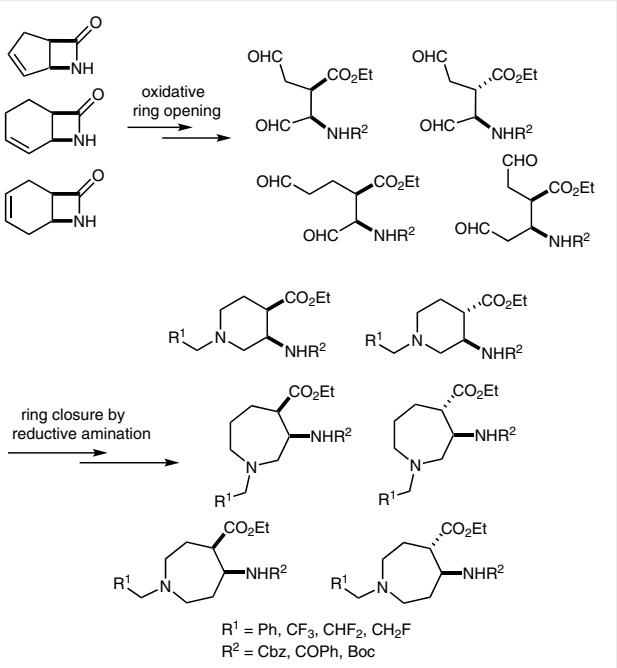
Scheme 2 Stereocontrolled synthesis of highly functionalized acyclic dienes from disubstituted cyclopentene stereoisomers via diformyl intermediates

Fluorinated organic molecules,[7] including fluorine-containing amino acid derivatives,[8] have generated increasing attention among medicinal chemists and such compounds have had a high impact on drug research over the last decade.[8] Our research group has applied various selective stereocontrolled strategies to gain access to a range of fluorinated β-amino acid derivatives.[8c] An approach to fluorinated scaffolds consisted of the transformation of diformyl cyclopentane β-amino esters derived from norbornene β-amino acid stereoisomers (Scheme 3).[9]



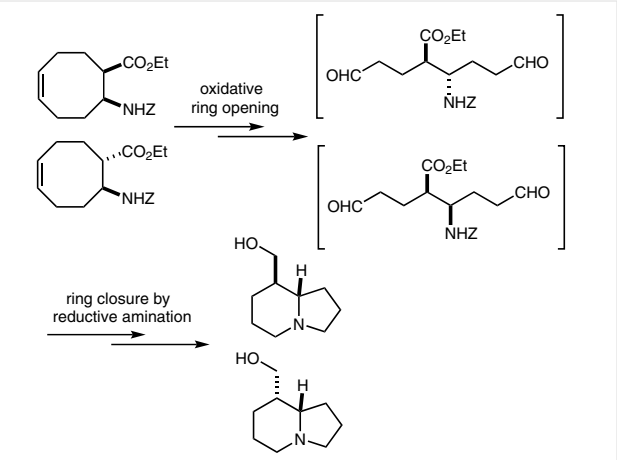
Scheme 3 Chemoselective synthesis of highly functionalized fluorinated scaffolds from disubstituted norbornenes via diformyl intermediates

Dialdehyde scaffolds resulting from oxidative ring cleavage of unsaturated bicyclic β-lactams were used as excellent precursors for the synthesis of *N*-heterocyclic β-amino esters (Scheme 4). Double reductive amination of diformyl β-amino esters with benzylamine or fluorinated amines afforded stereoisomers of piperidine or azepane β-amino esters.[8d,10a,b] Starting from di-*exo*- or di-*endo*-norbornene β-amino acids, the ring expansion with reductive amination resulted in the formation of *N*-bridged bicyclic β-amino esters.[8d,10c]



Scheme 4 Stereocontrolled synthesis of piperidine and azepane β-amino acid derivatives from unsaturated bicyclic β-lactams via diformyl intermediates

The reductive amination protocol was efficiently extended further to enable access to tashiromine and epitashiromine natural alkaloids. Diformyl amino ester stereoisomers, accessed from *cis*- or *trans*-cyclooctene β-amino esters, underwent intramolecular cyclization under reductive amination and led to the corresponding indolizidine alkaloids.[11]



Scheme 5 Stereocontrolled synthesis of natural products tashiromine and epitashiromine alkaloids from unsaturated bicyclic β-lactams via diformyl intermediates.

Notably, the configuration of the chiral centers of the final products prepared by using the above methodologies, based on the cyclization by reductive amination, were predetermined by the configurations of the stereocenters of the starting materials (Scheme 5).

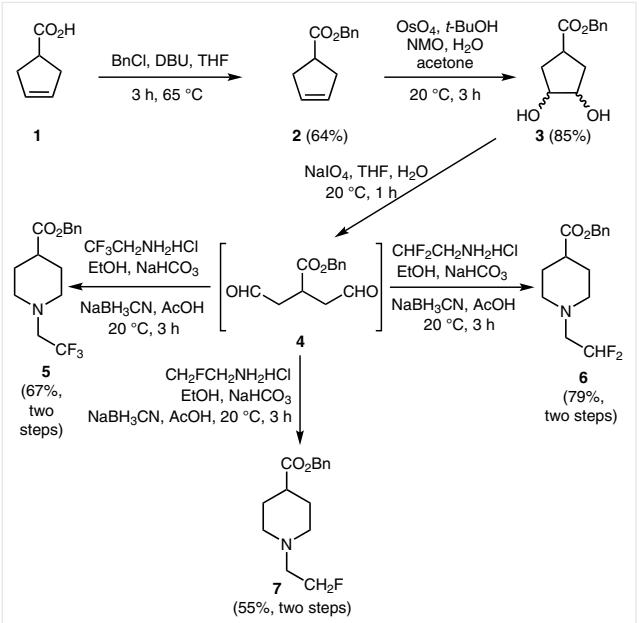
Results and Discussion

Our current aim is to offer an insight into the extension by generalization of the synthetic method summarized above. The protocol involves oxidative ring opening of various cycloalkenes followed by cyclization of the diformyl derivatives under reductive amination conditions, to synthesize various *N*-heterocyclic scaffolds that incorporate fluorinated entities in their structure. Taking into consideration the high biorelevance of *N*-heterocycles and organofluorine scaffolds, we decided to investigate the formation of fluorine-containing *N*-heterocyclic systems from various substituted dialdehydes. The latter compounds were derived from selected mono- or disubstituted cycloalkenes.

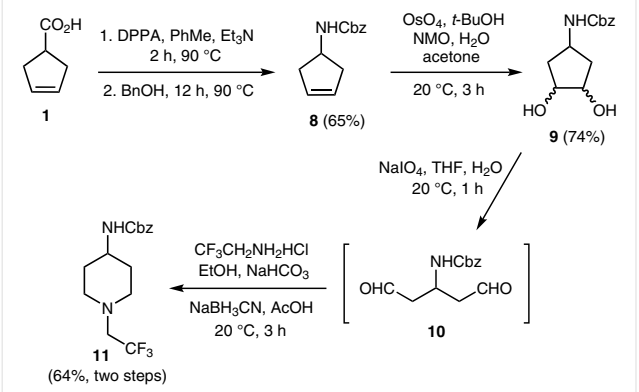
First, we explored the behavior of substituted five-membered cycloalkenes; namely, a cyclopentene carboxylate and a cyclopenteneamine. Cyclopentene benzyl ester **2** (prepared from the commercially available cyclopent-3-enecarboxylic acid **1**) was submitted to dialdehyde formation (Scheme 6). First, **2** was oxidized with *N*-methylmorpholine *N*-oxide (NMO)/OsO_4 to generate the corresponding vicinal diol derivatives **3** as a mixture of stereoisomers in nearly 1:1 ratio, which could not be separated either by crystallization or by chromatography. Given that the stereocenters are removed in the next oxidative ring cleavage step, the diastereoisomeric diol mixture **3** was used further without separation. Oxidation with $NaIO_4$ provided the corresponding unstable acyclic dialdehyde **4**, which was submitted without isolation or purification to a reductive ring-closure step. The latter reaction was initially performed with the commercially available fluorine-containing amine, 2,2,2-trifluoroethylamine. Diformyl intermediate **4**, upon reaction with the fluorine-containing amine noted above, followed by treatment with $NaBH_3CN$, furnished the corresponding trifluoromethylated piperidine derivative **5**.

The ring-closing protocol based on reductive amination of dialdehydes could be applied by using other fluorine-containing building blocks, which allowed access to other fluorinated piperidines. Illustrative is the treatment of diformyl derivative **4** with the commercially available 2,2-difluoromethylamine or 2-fluoroethylamine followed by reduction, affording the corresponding mono- or difluorinated piperidine derivatives **6** and **7** (Scheme 6).

Next, the substituent on the cyclopentene ring was changed from an ester to a protected amine. Commercially accessible unsaturated acid **1** was converted under Curtius reaction conditions into Cbz-protected amine **8**, the dihydroxylation of which furnished a 1:1 mixture of diol derivative **9** (Scheme 7). Again, this mixture was used in the next step without separation of the components, giving dialdehyde **10**. Without isolation, this unstable dialdehyde was transformed in the reaction with 2,2,2-trifluoroethylamine in the presence of $NaBH_3CN$ into trifluoromethylated piperidine **11** in good yield.



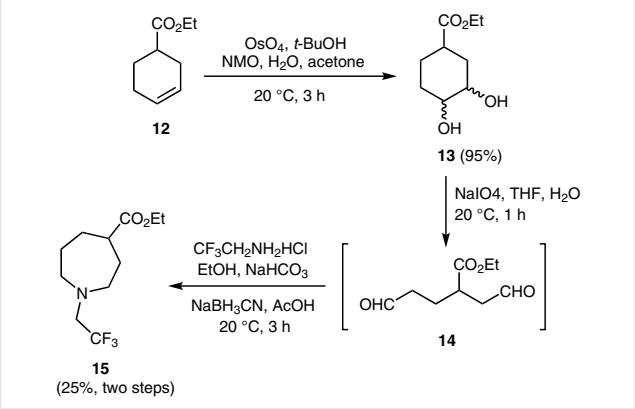
Scheme 6 Synthesis of functionalized piperidine derivatives **5–7** from cyclopentene carboxylate via a diformyl intermediate



Scheme 7 Synthesis of functionalized piperidine derivative **11** from cyclopentene carboxylate via a diformyl intermediate

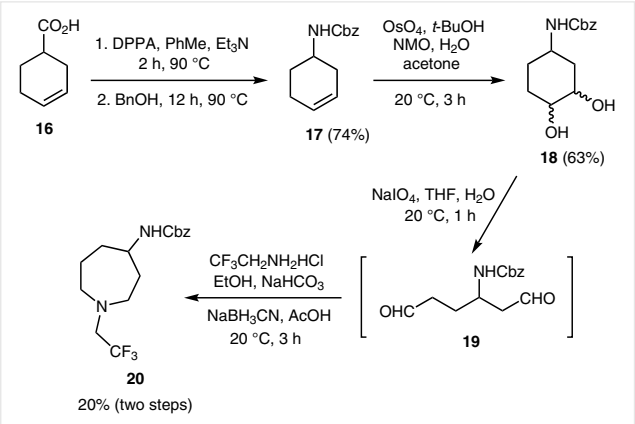
The transformation of dialdehyde substrates could be applied not only for the synthesis of piperidines but also for the construction of seven-membered functionalized *N*-heterocyclic systems. For this synthesis, we selected the six-membered analogues of the cyclopentene ester and amine studied above. Thus, commercially available ethyl cyclohex-3-enecarboxylate (**12**) was first subjected to dihydroxyl-

ation, yielding **13** as a mixture of diol diastereoisomers (1:1) (Scheme 8). Analogous to the five-membered counterpart, these could not be separated and, therefore, were used directly for ring opening with $NaIO_4$ affording the corresponding open-chain dialdehyde **14**. Unstable diformyl intermediate **14** was next converted without isolation on treatment with trifluorinated ethylamine into azepane derivative **15**.



Scheme 8 Synthesis of functionalized azepane derivative **15** from cyclohexene carboxylate via a diformyl intermediate

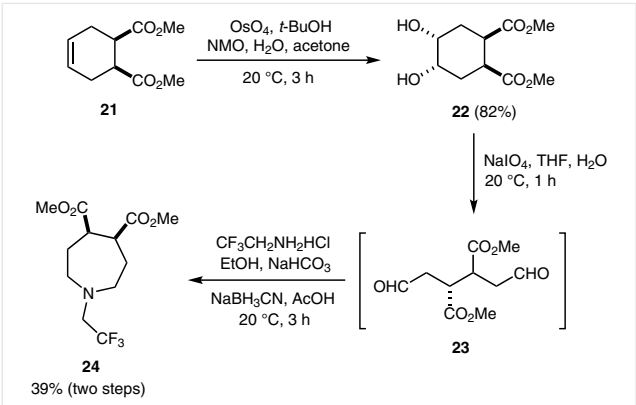
The synthesis of a fluorinated azepane bearing a Cbz-protected amine substituent could be achieved by starting from the commercially accessible cyclohex-3-enecarboxylic acid (**16**; Scheme 9). Cyclohexeneamine **17**, synthesized by Curtius reaction from **16**, led by dihydroxylation to diol mixture **18**, which was subjected to oxidative ring cleavage in the presence of $NaIO_4$.



Scheme 9 Synthesis of functionalized azepane derivative **20** from ethyl cyclohexene carboxylate via a diformyl intermediate

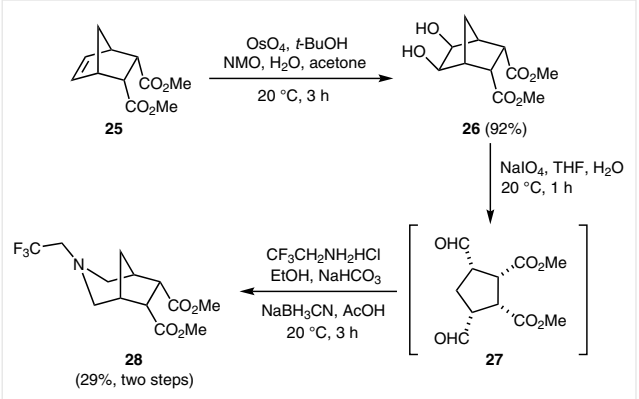
The formed unstable dialdehyde derivative **19** was further used without isolation. On treatment with 2,2,2-trifluroethylamine hydrochloride in EtOH, in the presence of $NaHCO_3$ and $NaBH_3CN$, ring closure involving reductive amination took place, resulting in the corresponding substituted azepane derivatives **20** containing a trifluoromethyl group (Scheme 9). Notably, formation of the seven-membered ring system proceeded with lower yield in comparison to those of the six-membered analogues.

As a continuation of the study, our next aim was to synthesize disubstituted trifluoromethylated *N*-heterocyclic derivatives. Dihydroxylation of the olefin bond of the commercially available cyclohexene *cis*-diester **21** afforded vicinal diol **22** (Scheme 10). Subsequent oxidative ring opening of **22** mediated by $NaIO_4$ followed by reductive ring closure with trifluoroethylamine afforded, via dialdehyde **23**, azepane diester **24**. Again, given that the stereocenters are not affected during the ring expansion procedure, the configurations of the chiral centers in **24** are predetermined by the structure of the starting material **21**.



Scheme 10 Synthesis of functionalized azepane derivative **24** from cyclohexene dicarboxylate via a diformyl intermediate

In view of the high physiological relevance of N-bridged bicyclic derivatives (e.g., cocaine, anatoxin-*a* analogues),[3a,e] our next aim was to extend the synthetic technique described above to the preparation of trifluoromethylated *N*-bicyclic systems. Thus, di-*endo*-norbornene dicarboxylate



Scheme 11 Synthesis of functionalized bicyclic derivative **28** from norbornene dicarboxylate via a diformyl intermediate

25[15] was transformed by dihydroxylation into diol derivative **26**, then the oxidative ring opening followed by reductive amination with trifluoroethylamine and $NaBH_3CN$, provided *N*-bicyclic diester **28** via diformyl derivative **27** (Scheme 11).

Conclusions

We have demonstrated the high value of substituted open-chain or alicyclic dialdehyde derivatives for the synthesis by double reductive amination of different types of *N*-heterocycles. In the current study we investigated the application of this synthetic procedure for the construction of functionalized fluorine-containing *N*-heterocyclic systems. The method includes the reaction of functionalized diformyl scaffolds, accessed by oxidative ring opening of various substituted cycloalkenes, with simple, commercially available fluorinated amines. Taking into consideration the availability of both a wide variety of cycloalkenes and functionalized primary amine building blocks, this convenient methodology might be further applied towards the synthesis of a series of functionalized saturated *N*-heterocycles.

The chemicals were purchased from Sigma-Aldrich and were used without further purification. The NMR spectra were recorded at 400 MHz with $CDCl_3$ or DMSO-d_6 as the solvent and tetramethylsilane as the internal standard. The solvents were used as received from the suppliers. Melting points were determined with a Kofler apparatus. Elemental analyses were recorded on a Perkin-Elmer CHNS-2400 Ser II elemental analyser. Silica gel 60 F_{254} was purchased from Merck.

Synthesis of N-Protected Cycloalkeneamines; General Procedure

To a solution of cycloalkencarboxylic acid (12 mmol) in anhydrous toluene (30 mL), Et_3N (12 mmol) and diphenylphosphoryl azide (DPPA, 12 mmol) were added and the resulting mixture was stirred for 2 h at r.t. and then for 1 h at 90 °C. A solution of benzyl alcohol (13.8 mmol) was added to this solution and the mixture was stirred overnight at 90 °C. The mixture was then diluted with EtOAc (40 mL) and washed with $NaHCO_3$ (2 × 20 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuo. The crude material was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

Esterification of Cycloalkenecarboxylic Acids; General Procedure

To a solution of cycloalkencarboxylic acid (9 mmol) in THF (50 mL), benzyl chloride (9 mmol) and DBU (22.5 mmol) were added and the solution was stirred for 3 h at 90 °C. Upon completion of the reaction, the mixture was diluted with EtOAc (40 mL) and washed with H_2O (3 × 30 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

Dihydroxylation of Substituted Cycloalkenes; General Procedure

To a stirred solution of substituted cycloalkene (10 mmol), OsO_4 (2% in *t*-BuOH, 0.3 mL), and NMO (1.2 equiv) were added in acetone (30 mL) and the resulting mixture was stirred at r.t. for 3 h. 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).

Fluorine-Containing *N*-Heterocyclic Derivatives by Ring Closure with Reductive Amination; General Procedure

To a stirred solution of diol (2 mmol), $NaIO_4$ (1.5 equiv) was added in THF/H_2O (25 mL/2 mL). After stirring the mixture for 1 h at 20 °C under an Ar atmosphere, H_2O was added until the precipitate dissolved (ca. 40 mL). The mixture was then extracted with CH_2Cl_2 (3 × 20 mL), the combined extract was dried over Na_2SO_4 and the resulting dialdehyde solution was evaporated. The crude product was used for the next reaction without purification. Fluorine-containing ethylamine hydrochloride (2 mmol), and $NaHCO_3$ (2 equiv) were added to the solution of the dialdehyde in EtOH (20 mL) and the mixture was stirred at 20 °C for 10 min. $NaBH_3CN$ (2 mmol) and AcOH (2 drops) were then added and stirring was continued for another 4 h at 20 °C. The reaction mixture was diluted with H_2O (20 mL), extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc).

Benzyl Cyclopent-3-enecarboxylate (2)[12]

Yield: 64% (1.15 g); yellow oil; R_f = 0.26 (*n*-hexane/EtOAc, 20:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.54–2.68 (m, 4 H, H-2, H-5), 3.15–3.26 (m, 1 H, H-1), 5.12 (s, 2 H, OCH_2), 5.68 (s, 2 H, CH=CH), 7.31–7.42 (m, 5 H, Ar-H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 36.8, 41.5, 66.5, 128.7, 128.9, 129.3, 129.8, 137.2, 179.3.

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.18; H, 6.97.

Benzyl Cyclopent-3-en-1-ylcarbamate (8)[13]

Yield: 65% (2.51 g); white solid; mp 31–32 °C; R_f = 0.33 (*n*-hexane/EtOAc 8:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.32–2.45 (m, 2 H, H-2, H-5), 2.73–2.86 (m, 2 H, H-2, H-5), 4.27–4.39 (m, 1 H, H-1), 5.22 (s, 2 H, OCH_2), 5.87 (s, 2 H, CH=CH), 7.47–7.70 (m, 6 H, Ar-H and N-H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 40.0, 51.1, 66.0, 120.8, 128.6, 129.2, 129.7, 138.1, 156.6.

Anal. Calcd for $C_{13}H_{14}O_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.85; H, 6.95; N, 6.44.

Benzyl Cyclohex-3-en-1-ylcarbamate (17)[14]

Yield: 74% (508 mg); yellow solid; mp 47–49 °C; R_f = 0.30 (*n*-hexane/EtOAc, 8:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.37–1.49 (m, 1 H, H-6), 1.76–1.84 (m, 1 H, H-5), 1.86–1.96 (m, 1 H, H-6), 2.04–2.11 (m, 2 H, H-2), 2.16–2.26 (m, 1 H, H-5), 3.47–3.58 (m, 1 H, H-1), 5.02 (s, 2 H, OCH_2), 5.54–5.66 (m, 2 H, CH=CH), 7.18–7.26 (br s, 1 H, N-H), 7.29–7.43 (m, 5 H, Ar-H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 25.4, 29.5, 32.3, 47.6, 66.4, 125.8, 127.4, 128.6, 129.2, 135.3, 155.5.

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.68; H, 7.39; N, 6.05.

Dimethyl (1*R,2*S**,3*R**,4*S**)-Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (25)**[15]

Yield: 89% (5.70 g); colorless oil; R_f = 0.42 (*n*-hexane/EtOAc, 4:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.23 (d, *J* = 8.8 Hz, 1 H, H-7), 1.37 (d, *J* = 8.8 Hz, 1 H, H-7), 3.05 (s, 2 H, H-2, H-3), 3.47 (s, 6 H, $COOCH_3$), 3.51 (s, 2 H, H-1, H-4), 6.12 (s, 2 H, CH=CH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 46.6, 48.2, 48.9, 51.9, 135.6, 173.1.

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.83; H, 6.70.

Dimethyl (1*R,2*S**,4*S**,5*R**)-4,5-Dihydroxycyclohexane-1,2-dicarboxylate (22)**

Yield: 82% (1.93 g); yellow oil; R_f = 0.38 (*n*-hexane/EtOAc 1:3).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.79–1.88 (m, 2 H, H-3, H-6), 1.89–1.97 (m, 2 H, H-3, H-6), 2.99 (s, 2 H, OH), 3.52–3.63 (m, 8 H, $COOCH_3$, H-1, H-2), 4.45 (d, *J* = 4.4 Hz, 2 H, H-4, H-5).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 30.7, 39.4, 52.3, 68.2, 174.5.

Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.70; H, 6.93.

Dimethyl (1*R,2*R**,3*S**,4*S**,5*S**,6*R**)-5,6-Dihydroxybicyclo[2.2.1]heptane-2,3-dicarboxylate (26)**[16]

Yield: 92% (1.07 g); colorless oil; R_f = 0.40 (*n*-hexane/EtOAc 1:4).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.18 (d, *J* = 10.0 Hz, 1 H, H-7), 1.83 (d, *J* = 10.0 Hz, 1 H, H-7), 2.23 (s, 2 H, OH), 3.05 (t, *J* = 2.14 Hz, 2 H, H-1, H-4), 3.54 (s, 6 H, $COOCH_3$), 3.88–3.92 (m, 2 H, H-2, H-3), 4.57–4.63 (m, 2 H, H-5, H-6).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 33.3, 44.6, 47.2, 52.0, 69.6, 172.8.

Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.07; H, 6.59.

Benzyl [1-(2,2,2-Trifluoroethyl)azepan-4-yl]carbamate (20)

Yield: 20% (151 mg); yellow oil; R_f = 0.25 (*n*-hexane/EtOAc, 3:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.41–1.96 (m, 6 H, H-3, H-5, H-6), 2.68–2.89 (m, 4 H, 2-H, 7-H), 3.17–3.29 (m, 2 H, CH_2-CF_3), 3.48–3.60 (m, 1 H, H-4), 4.99 (s, 2 H, OCH_2), 7.16–7.23 (br s, 1 H, N-H), 7.27–7.39 (m, 5 H, Ar-H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 25.2, 34.1, 35.6, 51.7, 52.0, 56.1, 57.5 and 57.8 and 58.1 and 58.3 (q, $^2J_{C-F}$ = 29.05, CCF_3), 65.9, 125.9 (q, $^1J_{C-F}$ = 260.0 Hz, CF_3), 128.3, 128.6, 129.2, 138.2, 156.0.

^{19}F NMR (100 MHz, DMSO-d_6): δ = –69.4.

MS (ESI): *m*/*z* = 331.3 [M + 1].

Anal. Calcd for $C_{16}H_{21}F_3N_2O_2$: C, 58.17; H, 6.41; N, 8.48. Found: C, 58.15; H, 6.40; F, 17.23; N, 8.45.

Ethyl 1-(2,2,2-Trifluoroethyl)azepane-4-carboxylate (15)

Yield: 25% (2.045 g); colorless oil; R_f = 0.30 (*n*-hexane/EtOAc, 10:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.17 (t, *J* = 7.06 Hz, 3 H, CH_3), 1.47–1.77 (m, 4 H, H-5, H-6), 1.80–1.92 (m, 2 H, H-3), 2.51–2.57 (m, 1 H, H-4), 2.72–2.93 (m, 4 H, H-2, H-7), 3.24–3.28 (m, 2 H, CF_3CH_2), 4.00–4.09 (m, 2 H, CH_2CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 15.0, 27.2, 30.1, 31.6, 43.8, 53.7, 55.9, 57.0 and 57.3 and 57.6 and 57.9 (q, $^2J_{C-F}$ = 29.2, CCF_3), 60.6, 128.6 (q, $^1J_{C-F}$ = 280 Hz, CF_3), 176.6.

^{19}F NMR (100 MHz, DMSO-d_6): δ = –69.5.

MS (ESI): *m*/*z* = 254.2 [M + 1].

Anal. Calcd for $C_{11}H_{18}F_3NO_2$: C, 52.17; H, 7.16; N, 5.53. Found: C, 52.14; H, 7.15; F, 22.48; N, 5.52.

Benzyl [1-(2,2,2-Trifluoroethyl)piperidin-4-yl]carbamate (11)

Yield: 64% (482 mg); white solid; mp 63–66 °C; R_f = 0.18 (*n*-hexane/EtOAc, 4:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.35–1.48 (m, 2 H, H-3, H-5,), 1.71 (d, *J* = 13.2 Hz, 2 H, H-3, H-5), 2.36 (t, *J* = 11.6 Hz, 2 H, H-2, H-6), 2.86 (d, *J* = 12.4 Hz, 2 H, H-2, H-6), 3.06–3.18 (m, 2 H, CH_2CF_3), 5.00 (s, 2 H, OCH_2), 7.21 (br s, 1 H, N-H), 7.27–7.40 (m, 5 H, Ar-H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 32.5, 48.2, 53.3, 57.3 and 57.5 and 57.8 and 58.1 (q, $^2J_{C-F}$ = 28.0 Hz, CCF_3), 66.0, 128.3 (q, $^1J_{C-F}$ = 260 Hz, CF_3), 128.6, 129.2, 138.2, 156.2.

^{19}F NMR (100 MHz, DMSO-d_6): δ = –68.1.

MS (ESI): *m*/*z* = 317.3 [M + 1].

Anal. Calcd for $C_{15}H_{19}F_3N_2O_2$: C, 56.96; H, 6.05; N, 8.86; found: C, 56.93; H, 6.04; F, 18.00; N, 8.84.

Benzyl 1-(2,2,2-Trifluoroethyl)piperidine-4-carboxylate (5)

Yield: 67% (514 mg); brown oil; R_f = 0.33 (*n*-hexane/EtOAc, 10:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.53–1.65 (m, 2 H, H-3, H-5), 1.77–1.85 (m, 2 H, H-3, H-5), 2.34–2.43 (m, 3 H, H-2, H-4, H-6), 2.82–2.90 (m, 2 H, H-2, H-6), 3.08–3.18 (m, 2 H, CH_2CF_3), 5.10 (s, 2 H, OCH_2), 7.29–7.40 (m, 5 H, Ar-H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 28.8, 40.5, 53.4, 57.4 and 57.7 and 58.0 and 58.3 (q, $^2J_{C-F}$ = 29.0 Hz, CCF_3), 66.3, 125.5 (q, $^1J_{C-F}$ = 275.6 Hz, CF_3), 128.6, 128.8, 129.3, 137.2, 174.9.

^{19}F NMR (100 MHz, DMSO-d_6): δ = –69.1.

MS (ESI): *m*/*z* = 302.3 [M + 1].

Anal. Calcd for $C_{15}H_{18}F_3NO_2$: C, 59.79; H, 6.02; N, 4.65. Found: C, 59.75; H, 6.00; F, 18.90; N, 4.64.

Dimethyl (4*R,5*S**)-1-(2,2,2-Trifluoroethyl)azepane-4,5-dicarboxylate (24)**

Yield: 39% (303 mg); colorless oil; R_f = 0.12 (*n*-hexane/EtOAc, 10:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.84–1.95 (m, 2 H, H-3, H-6), 1.95–2.09 (m, 2 H, H-3, H-6), 2.71–2.86 (m, 4 H, H-2, H-7), 2.98–3.07 (m, 2 H, H-4, H-5), 3.17–3.28 (m, 2 H, CH_2CF_3), 3.57 (s, 6 H, $COOCH_3$).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 28.8, 44.5, 52.2, 53.3, 57.6 and 57.9 and 58.2 and 58.5 (q, $^2J_{C-F}$ = 29.2 Hz, CCF_3), 125.6, 128.4 (q, $^1J_{C-F}$ = 279.6 Hz, CF_3), 174.1.

^{19}F NMR (100 MHz, DMSO-d_6): δ = –69.7.

MS (ESI): *m*/*z* = 298.2 [M + 1].

Anal. Calcd for $C_{12}H_{18}F_3NO_4$: C, 48.48; H, 6.10; F, 19.17; N, 4.71. Found: C, 48.45; H, 6.09; F, 19.15; N, 4.70.

Dimethyl (1*R,5*S**,6*R**,7*R**)-3-(2,2,2-Trifluoroethyl)-3-azabicyclo[3.2.1]octane-6,7-dicarboxylate (28)**

Yield: 29% (254 mg); white solid; mp 52–55 °C; R_f = 0.35 (*n*-hexane/EtOAc, 8:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.48 (d, *J* = 12 Hz, 1 H, H-8), 1.60–1.68 (m, 1 H, H-8), 2.29 (s, 2 H, H-5, H-5), 2.54 (s, 2 H, H-2, H-4), 2.95–3.05 (m, 2 H, CH_2CF_3), 3.13–3.18 (m, 2 H, H-2, H-4), 3.23–3.27 (m, 2 H, 6-H, 7-H), 3.54 (s, 6 H, $COOCH_3$).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 37.8, 38.2, 46.0, 51.6, 55.5, 57.1 and 57.4 and 57.7 and 58.0 (q, $^2J_{C-F}$ = 29.0 Hz, CCF_3), 128.3 (q, $^1J_{C-F}$ = 270 Hz, CF_3), 172.2.

^{19}F NMR (100 MHz, DMSO-d_6): δ = –66.9.

MS (ESI): m/z = 310.3 [M + 1].

Anal. Calcd for $C_{13}H_{18}F_3NO_4$: C, 50.48; H, 5.87; F, 18.43; N, 4.53. Found: C, 50.45; H, 5.86; F, 18.40; N, 4.52.

Benzyl 1-(2,2-Difluoroethyl)piperidine-4-carboxylate (6)

Yield: 79% (566 mg); colorless oil; R_f = 0.18 (*n*-hexane/EtOAc, 8:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.41–1.57 (m, 2 H, H-3, H-5), 1.64–1.78 (m, 2 H, H-3, H-5), 2.05–2.16 (m, 2 H, H-2, H-6), 2.18–2.32 (m, 1 H, H-4), 2.49–2.64 (td, J = 15.7, 4.28 Hz, 2 H, CH_2CHF), 2.66–2.78 (m, 2 H, H-2, H-6), 4.99 (s, 2 H, OCH_2), 5.78–6.16 (tt, J = 55.7, 4.35 Hz, 1 H, CHF_2), 7.16–7.35 (m, 5 H, Ar-H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 28.8, 40.7, 53.7, 60.0 and 60.2 and 60.5 (t, $^2J_{C-F}$ = 24.1 Hz, $CCHF_2$), 66.2, 114.40 and 116.8 and 119.2 (t, $^1J_{C-F}$ = 237.6 Hz, CHF_2), 128.6, 128.8, 129.3, 137.2, 174.9.

^{19}F NMR (100 MHz, DMSO-d_6): δ = –115.1.

MS (ESI): m/z = 284.33 [M + 1].

Anal. Calcd for $C_{15}H_{19}F_2NO_2$: C, 63.59; H, 6.76; F, 13.41; N, 4.94. Found: C, 63.56; H, 6.75; F, 13.39; N, 4.93.

Benzyl 1-(2-Fluoroethyl)piperidine-4-carboxylate (7)

Yield: 55% (290 mg); colorless oil; R_f = 0.25 (*n*-hexane/EtOAc, 1:4).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.52–1.68 (m, 2 H, H-3, H-5), 1.76–1.89 (m, 2 H, H-3, H-5), 2.01–2.14 (m, 2 H, H-2, H-6), 2.30–2.41 (m, 1 H, H-4), 2.52–2.66 (dt, J = 28.3, 4.9 Hz, 2 H, CH_2CH_2F), 2.77–2.86 (m, 2 H, H-2, H-6), 4.41–4.60 (dt, J = 47.8, 4.9 Hz, 2 H, CH_2F), 5.01 (s, 2 H, OCH_2), 7.29–7.41 (m, 5 H, Ar-H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 28.8, 41.0, 53.4, 58.5 and 58.7 (d, $^2J_{C-F}$ = 20.0 Hz, CCH_2F), 66.2, 81.9 and 83.6 (d, $^1J_{C-F}$ = 163.5 Hz, CH_2F), 128.6, 128.8, 129.3, 137.2, 175.0.

^{19}F NMR (100 MHz, DMSO-d_6): δ = –216.8.

MS (ESI): m/z = 266.32 [M + 1].

Anal. Calcd for $C_{15}H_{20}FNO_2$: C, 67.90; H, 7.60; F, 7.16; N, 5.28. Found: C, 67.88; H, 7.59; F, 7.15; N, 5.27.

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Supporting Information

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