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Lucas Bacheley, Ricardo Molina Betancourt, Rathies Ravindra, Gérard Guillamot, Phannarath Phansavath, et al.. Asymmetric Synthesis of Monofluorinated Carbocyclic Alcohols and Vicinal Difluorinated Heterocycles and Carbocycles. *European Journal of Organic Chemistry*, 2023, 26 (25), 10.1002/ejoc.202300383 . hal-04270061

HAL Id: hal-04270061

<https://hal.science/hal-04270061v1>

Submitted on 18 Dec 2023

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Asymmetric Synthesis of Monofluorinated Carbocyclic Alcohols and Vicinal Difluorinated Heterocycles and Carbocycles

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Dedication ((optional))

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Abstract: A straightforward method to access novel families of enantioenriched *cis*-monofluorinated carbocyclic alcohols has been developed through ATH/DKR in up to 97% yield, up to 99:1 dr and enantioinductions up to 97% ee. *Trans*-difluorinated indans, tetrahydronaphthalenes, tetrahydroquinolines and chromans have been synthesized as well by deoxofluorination of the corresponding *cis*-fluoro alcohols. The reaction was performed on a series of variously substituted 3-fluorochromanols, 3-fluorotetrahydroquinolins, 2-fluoro inden-1-ols and 2-fluoro 1,2,3,4-tetrahydronaphthalen-1-ols in up to 86% yields, with diastereoselectivities up to 97:3 and enantioselectivities up to >99% ee.

Introduction

The fine-tuning of physico-chemical properties of a molecule is a central topic of modern drug design and development. Amid the tools that the medicinal chemist has in hands for this important purpose, fluorine has proven itself as extremely valuable due to its intrinsic characteristics of low Van der Waals radius and polarity-bond inversion.^[1,2] This ranks fluorine as a hydrogen isostere and allows to modulate properties while unaltering the molecular volume. From the different patterns in which fluorine can be added to a molecule, the vicinal 1,2-difluoro one can bring unique contributions thanks to the *gauche* effect.^[3,4] This stereoelectronic phenomenon where the F-C-C-F dihedral angle is of 60°, translates into an increase of polarity and spatial pre-arrangement of the molecule.

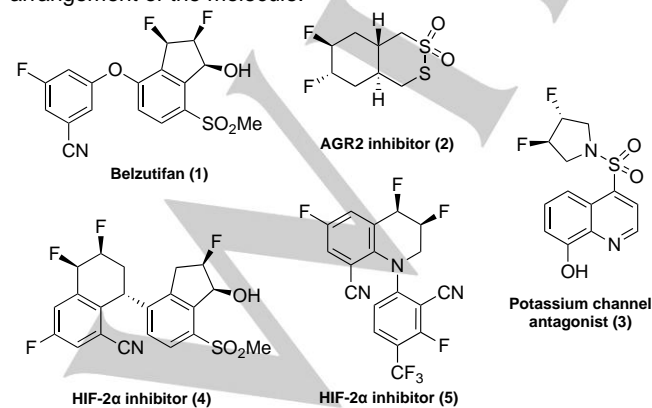
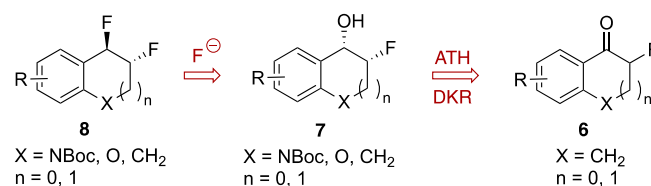


Figure 1. Compounds of interest bearing the vicinal difluoro motif.

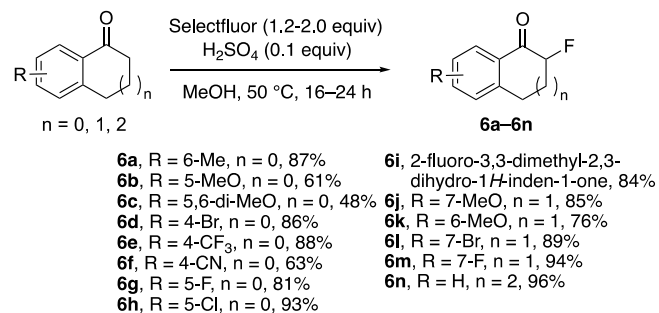
Furthermore, the *vic*-difluoro group is present in a series of biological active compounds (Figure 1). Belzutifan (**1**) is an active molecule for the treatment of von Hippel–Lindau disease-associated renal cell carcinoma and has been approved in 2021 by the FDA for medical use.^[5] Compound (**2**) is an inhibitor of AGR2, a protein disulphide isomerase involved in the pathway of several cancer diseases.^[6] The quinolinol (**3**) is an antagonist of the potassium channel^[7] and can thus treat arrhythmia and molecules (**4**) and (**5**) are inhibitors of the hypoxia-inducible factor subunit α (HIF-2 α) and can be used in the treatment of cancer and inflammatory diseases.^[8] The vicinal difluoro pattern can be sequentially formed through the deoxofluorination of chiral diols or diol derivatives obtained from either the chiral pool or *via* an asymmetric oxidative reaction (epoxidation or dihydroxylation).^[9-17] On the other hand, the direct introduction of the vicinal difluoro motif has been described using an asymmetric, catalytic 1,2-difluorination of alkenes^[18,19] or by I(I)/I(III) catalysis.^[20] Because of the important features of the motif described above, and as a continuation of our work directed towards the preparation of valuable enantioenriched building blocks,^[21-24] we report herein the synthesis of novel families of enantioenriched *cis*-monofluorinated carbocyclic alcohols and *trans*-difluorinated indans, 1,2,3,4-tetrahydronaphthalenes, *N*-Boc tetrahydroquinolines and chromans **8**, by deoxofluorination of the corresponding *cis*-fluoro alcohols **7** (Scheme 1). The enantiomerically enriched 2-fluoro inden-1-ol (**7**, X = CH₂, n = 0) and 2-fluoro 1,2,3,4-tetrahydronaphthalen-1-ol (**7**, X = CH₂, n = 1) derivatives would result from transition metal-catalyzed asymmetric transfer hydrogenation/dynamic kinetic resolution (ATH/DKR)^[25-32] of 2-fluoro-2,3-dihydro-1*H*-inden-1-ones and 2-fluoro-3,4-dihydronaphthalen-1(2*H*)-ones **6** whereas we previously achieved the preparation of enantioenriched fluoro chromanols (**7**, X = O)^[33] and *N*-Boc fluoro hydroxy dihydroquinolines (**7**, X = NBoc)^[34] derivatives.



Scheme 1.

Results and Discussion

The study began with the preparation of the racemic 2-fluoro-2,3-dihydro-1*H*-inden-1-ones, 2-fluoro-3,4-dihydronaphthalen-1(2*H*)-ones and 6-fluoro-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one **6a–6n** bearing diverse electron-donating or electron-withdrawing groups on the aryl ring by fluorination with Selectfluor^[35,36] (Scheme 2).



Scheme 2. Preparation of compounds **6a–6n**.

Compound **6a** then served as a standard substrate for optimization of the asymmetric transfer hydrogenation reaction mainly consisting of a screening of the catalyst (Table 1).

Table 1. Catalyst screening for the ATH/DKR of **6a**.^[a]

Entry	Catalyst	HCO ₂ H/Et ₃ N	time (h)	Yield ^[b] (%)	dr ^[c] (<i>cis:trans</i>)	ee ^[d] (%)
1	(<i>R,R</i>)- A	1:1	5	98	90:10	85
2	(<i>R,R</i>)- B	1:1	5	92	95:5	94
3	(<i>R,R</i>)- C	1:1	8	93	94:6	95
4	(<i>S,S</i>)- D	1:1	7	91	91:9	62 ^[e]
5	(<i>R,R</i>)- E	1:1	24	90	98:2	96
6	(<i>R,R</i>)- F	1:1	1	89	77:23	57
7 ^[e]	(<i>R,R</i>)- E	1:1	19	90	98:2	95

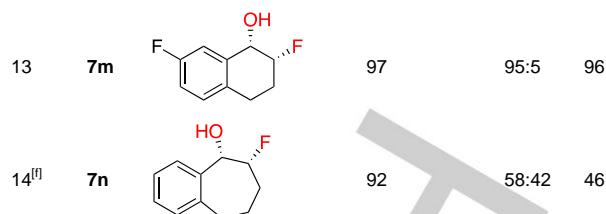
[a] Reaction conditions: **6a** (0.49 mmol), catalyst (0.5 mol%), HCO₂H/Et₃N (1:1) (15 equiv), MeCN (0.3 M), 40 °C. [b] Isolated yield. [c] Determined by ¹H NMR spectroscopy of the crude product after the ATH reaction. [d] The ee for

the *cis*-product was determined by SFC analysis. [e] ee for *ent*-**7a** [f] Reaction carried out under neat conditions at 30 °C.

Based on previous ATH studies carried out in the group, the reduction of *rac*-**6a** was conducted in acetonitrile at 40 °C using 0.5 mol% of commercially available complex (*R,R*)-**A**, (*R,R*)-**B**, (*R,R*)-**C**, (*S,S*)-**D**, (*R,R*)-**E**, and home-made (*R,R*)-**F**^[37,38] and 15 equiv of a formic acid/triethylamine (1:1) mixture acting as the hydrogen source. Under these conditions, high yields were observed in all cases for the reduced product *cis*-**7a** but with varying diastereomeric ratios and enantioselectivities. The use of the (*R,R*)-TsDENEb complex {(*R,R*)-**A**} allowed the asymmetric reduction to proceed with a high dr of 90:10 and an enantioselectivity of 85% for *cis*-**7a** (Table 1, entry 1). However the ATD/DKR of **6a** was more efficient with the ruthenium complex [(*R,R*)-RuCl(*p*-cymene)TsDPEN] {(*R,R*)-**B**} that led to higher dr and ee values of 95:5 and 94%, respectively (Table 1, entry 2). Whereas the parent Ru complex (*R,R*)-**C** afforded similar results in terms of diastereo- and enantioselectivities (Table 1, entry 3), a lower enantioselectivity of 63% was observed with complex (*S,S*)-**D** (Table 1, entry 4). When the reaction was performed with complex (*R,R*)-**E**, a high diastereomeric ratio of 98:2 was achieved alongside a high enantiomeric excess of 96% (Table 1, entry 5). The rhodium complex (*R,R*)-**F** gave a diastereomeric ratio of 77:23 with an enantioselectivity of 57% ee (Table 1, entry 6). Finally, we found the reaction rate increased when the ATH was operated under neat conditions even at a lower temperature of 30 °C (Table 1, entry 7). From this survey, we chose to set the optimized reaction conditions under the more sustainable neat conditions using complex (*R,R*)-**E** (0.5 mol%) as the precatalyst, HCO₂H/Et₃N (1:1) (15 equiv) as the hydrogen source at 30 °C. These conditions were used to access a series of enantioenriched 2-fluoro inden-1-ols, 2-fluoro 1,2,3,4-tetrahydronaphthalen-1-ols and 6-fluoro-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ol derivatives **7a–7n** from compounds **6a–6n** (Table 2). The ruthenium-catalyzed asymmetric transfer hydrogenation of compounds **6b–6c** carrying MeO electron-donating group(s) proceeded in 74% and 81% yields with diastereomeric ratios of 93:7–96:4 and ee values of 82% and 73%, respectively (Table 2, entries 2 and 3). Likewise, the asymmetric reduction/DKR of 2-fluoro-2,3-dihydro-1*H*-inden-1-ones **6d–6h** having electron-withdrawing substituents such as CF₃, CN, F, Cl, or Br on various positions of the aromatic ring delivered the corresponding fluoroalcohols **7d–7h** in 72–94% yields and with high levels of diastereo- and enantioselectivities (94:6–99:1 dr, 91–97% ee) (Table 2, entries 4–8). In addition, reaction of 2-fluoro-3,3-dimethyl-2,3-dihydro-1*H*-inden-1-one **6i** under the optimized conditions allowed the efficient formation of a product **7i** bearing a *gem*-dimethyl moiety on the indane ring (Table 2, entry 9). On the other hand, the ATH/DKR of the 2-fluoro-3,4-dihydronaphthalen-1(2*H*)-one derivatives **6j–6m** furnished the corresponding 2-fluoro 1,2,3,4-tetrahydronaphthalen-1-ol derivatives **7j–7m** in 78–97% yields with diastereomeric ratios of 91:9–95:5 and ee values of 95–97% (Table 2, entries 10–13). Finally, the asymmetric transfer hydrogenation of 6-fluoro-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one **6n** bearing a 7-membered carbocycle was studied. Although a good yield of 92% for **7n** could be attained in the presence of 2 mol% of the complex (*R,R*)-**E**, the reduction proceeded in only 58:42 dr and 46% ee (Table 2, entry 14).

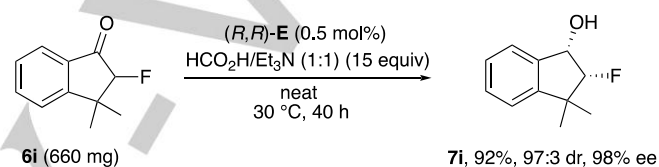
Table 2. Ruthenium-catalyzed ATH/DKR of compounds **6a–6n**.^[a]

Entry	Product	Yield ^[b] (%)	dr ^[c]	ee (%) ^[d]
1	7a	90	98:2	95
2 ^[e]	7b	74	93:7	82
3 ^[f]	7c	81	96:4	73
4	7d	93	98:2	95
5	7e	93	99:1	94
6	7f	90	94:6	91
7 ^[e]	7g	72	98:2	97
8	7h	94	96:4	97
9	7i	92	96:4	97
10	7j	90	93:7	97
11 ^[e,f]	7k	78	91:9	95
12	7l	89	94:6	96

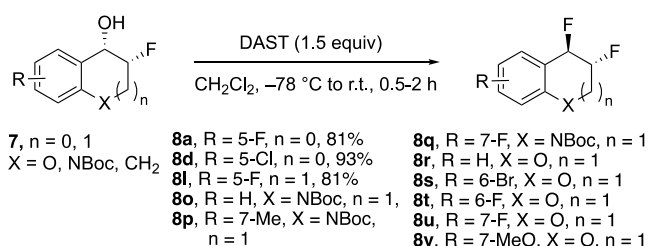
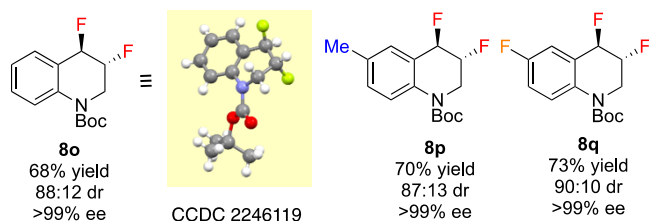


[a] Reaction conditions: **6a–6n** (100 mg), (*R,R*)-**E** (0.5 mol%), HCO₂H/Et₃N (1:1) (15 equiv), neat, 30 °C, 5–54 h, see experimental section for details. [b] Isolated yield. [c] Determined by ¹H NMR spectroscopy of the crude product after the ATH reaction. [d] The ee for the *cis*-product was determined by SFC analysis. [e] Incomplete conversion. [f] 2 mol%

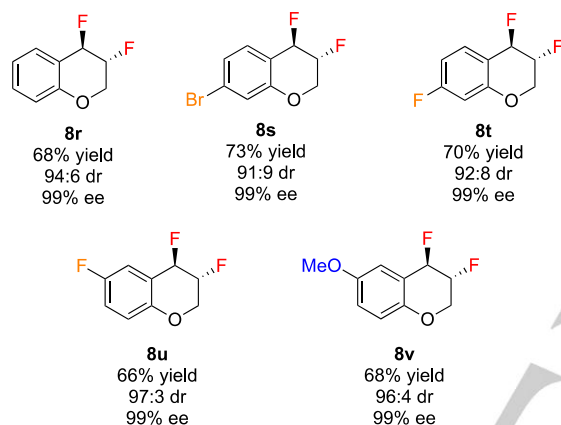
The efficiency of the ATH/DKR process was supported by a scale-up experiment performed on compound **6i** (Scheme 3). Under the optimized reaction conditions, the ruthenium-catalyzed asymmetric reduction carried out on 660 mg of the fluoro-ketone delivered the desired fluoro alcohol in 92% yield, with slightly higher stereoselectivities (97:3 dr, 98% ee).

**Scheme 3.** Scale-up experiment.

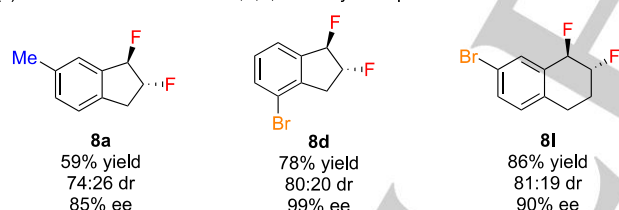
Next, considering the crucial role of difluorinated compounds in medicinal chemistry, we decided to explore the deoxofluorination reaction of nitrogen and oxygen-containing monofluorinated heterocyclic alcohols (Scheme 4). The reaction was run in dichloromethane from –78 °C to rt in the presence of 1.5 equiv of diethylaminosulfur trifluoride (DAST)^[39,40] as a nucleophilic fluorinating reagent. In this context, **8o–8q** were obtained in 68–73% yields starting from the corresponding *cis*-monofluorinated cyclic alcohols but a slight erosion of the diastereomeric ratio was observed in all cases (Scheme 4(a)). Higher diastereoselectivities ranging from 91:9 to 97:3 were attained for the chromanone series and compounds **8r–8v** bearing electron-donating and withdrawing substituents on the aryl part of the scaffold were prepared in 66–73% yields with excellent enantioinductions up to 99% (Scheme 4(b)). Finally, having substituted enantiomerically enriched 2-fluoro inden-1-ol and 2-fluoro 1,2,3,4-tetrahydronaphthalen-1-ol derivatives **7** in hand, the deoxofluorination reaction was performed on a selection of *cis*-monofluorinated carbocyclic alcohols **7a**, **7d** and **7l** to deliver the *trans*-difluorinated indan and 1,2,3,4-tetrahydronaphthalene derivatives **8a**, **8d** and **8l** in 59–86% yields with 74:26–81:19 diastereoselectivities and up to 99% ee (Scheme 4(c)). As the 1,2-difluorinated products were produced efficiently and with good yields using DAST for the deoxofluorination reaction, we did not explore other fluorination agents. The absolute configuration of the major diastereomer of the *N*-Boc tetrahydroquinoline **8o** was unambiguously assigned as (3*R*,4*R*) by X-ray crystallographic analysis. By analogy, we conjectured that the other products resulting from the described deoxofluorination followed the same trend.

(a) Difluorinated *N*-Boc tetrahydroquinolines:

(b) Difluorinated chromans:



(c) Difluorinated indans and 1,2,3,4-tetrahydronaphthalene:

**Scheme 4.** Synthesis of vicinal difluorinated carbocyclic and heterocyclic compounds.

Conclusion

In summary, a straightforward method to access enantiomerically and diastereomerically enriched *cis*-monofluorinated carbocyclic alcohols as well as *trans*-difluorinated indans, tetrahydronaphthalenes, tetrahydroquinolines and chromans has been developed. The ruthenium-catalyzed ATH/DKR of 2-fluoro-2,3-dihydro-1*H*-inden-1-ones and 2-fluoro-3,4-dihydronaphthalen-1(2*H*)-ones proceeded efficiently in the presence of complex (*R,R*)-**E** and HCO₂H/Et₃N (1:1) as the hydrogen source to give the corresponding *cis*-monofluorinated carbocyclic alcohols in high yields and diastereo- and enantioselectivities. On the other hand, the deoxofluorination reaction was performed successfully on a series of diversely substituted 3-fluorochromanols, 3-

fluorotetrahydroquinolins, 2-fluoro inden-1-ol and 2-fluoro 1,2,3,4-tetrahydronaphthalen-1-ol derivatives with 59–86% yields, diastereoselectivities up to 97:3 and enantioselectivities up to >99%, giving access to vicinal difluorinated heterocycles and carbocycles as valuable building blocks.

Experimental Section

General procedure for the asymmetric transfer hydrogenation/dynamic kinetic resolution of compounds (6): In a dried round-bottom tube under argon was added freshly distilled triethylamine (9.14 mmol, 1.27 mL, 15.0 equiv.) at 0 °C. Then formic acid (99%, Thermo Fischer) (9.14 mmol, 345 μ L, 15.0 equiv.) was added dropwise and the mixture was stirred for 5 min at 0 °C and allowed to warm at room temperature. Complex (*R,R*)-**E** (3.5 μ mol, 0.85 mg, 0.005 equiv.) was added followed by the α -fluorinated ketone (0.61 mmol, 100 mg, 1.0 equiv.) under argon. The reaction mixture was stirred at 30 °C for the time needed to achieve a complete conversion (5–54 h). The reaction mixture was then diluted in CH₂Cl₂ (5 mL) and water (5 mL). The aqueous phase was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The diastereomeric ratio was determined by ¹H NMR analysis of the crude product. The remaining solid was diluted in CH₂Cl₂, filtered over a pad of silica gel, rinsed with CH₂Cl₂ (100 mL) and concentrated under vacuum. When an incomplete conversion was observed, the residue was purified with a flash column chromatography on silica gel (petroleum ether/EtOAc). The enantiomeric excess was determined by SFC or HPLC analysis.

General procedure for the synthesis of compounds (8) by deoxofluorination: To a –78 °C solution of fluoro-alcohol (0.3 M in CH₂Cl₂, 0.24 mmol, 1.0 equiv.) in a round-bottom tube set under argon, DAST (0.36 mmol, 48 μ L 1.5 equiv.) was slowly added by syringe over 5 min. The mixture was stirred at –78 °C for 2 h. The reaction mixture was allowed to warm to room temperature and quenched with 5 mL of saturated NH₄Cl aqueous solution. The mixture was then extracted with CH₂Cl₂ (2 x 10 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The pure product was isolated by flash column chromatography on silica gel (petroleum ether/EtOAc 98:2 for the difluorinated carbocycles, 95:5 for the difluorinated chromanols, 85:15 for the difluorinated tetrahydroquinolols).

Acknowledgements

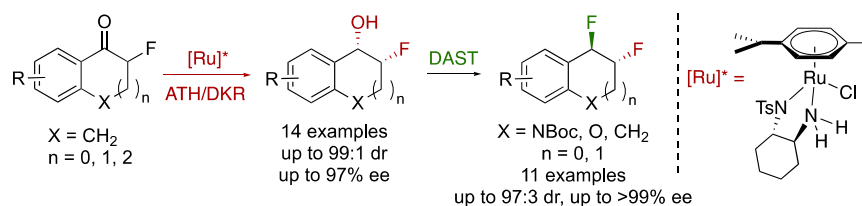
This work was supported by the Ministère de l'Éducation Nationale, de l'Enseignement Supérieur, de la Recherche et de l'Innovation (MESRI) and the Centre National de la Recherche Scientifique (CNRS). L. B. is grateful to SEQENS for a grant (2021–2024). We gratefully acknowledge the MESRI for a grant to R. M. B. (2019–2022). We thank G. Gontard (Sorbonne Université, Paris) for solving the X-ray structure of compound **8o**, Dr C. Fosse (Chimie ParisTech) and the MS3U platform (Sorbonne Université, Paris, France) for HRMS analysis.

Keywords: Asymmetric Transfer Hydrogenation • Catalysis • Fluorine • Vicinal difluoride • Ruthenium

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Entry for the Table of Contents



A straightforward access to novel families of enantioenriched *cis*-monofluorinated carbocyclic alcohols has been developed through ruthenium-catalyzed asymmetric transfer hydrogenation/dynamic kinetic resolution that proceeded in high diastereo- and enantioselectivities. Valuable enantioenriched vicinal difluorinated heterocycles and carbocycles such as *trans*-difluorinated indans, tetrahydronaphthalenes, tetrahydroquinolines and chromans have been synthesized as well by deoxofluorination of the corresponding *cis*-fluoro alcohols.