Atom Efficient Synthesis of Selectively Difluorinated Carbocycles through a Gold(I) Catalyzed Cyclization

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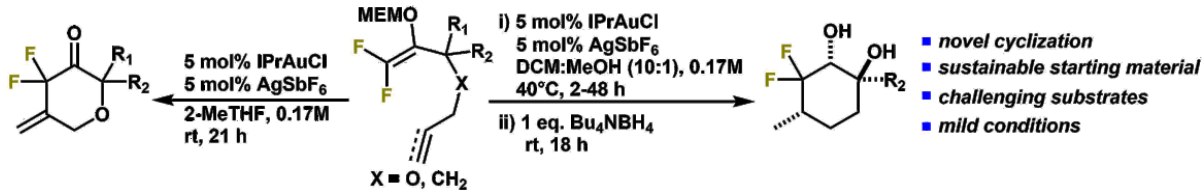


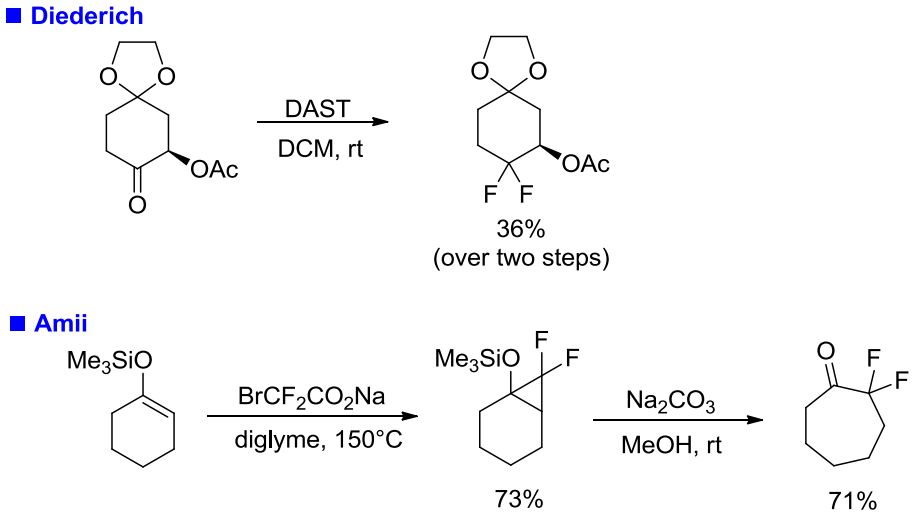
Abstract

The intramolecular carbocyclization of difluorinated enol acetals has been achieved for the first time using gold(I) catalysis. Difluorinated enol acetals bearing a pendant alkene group can be cyclized and reduced in one pot to form fluorinated diol motifs. Alternatively, the cyclization of terminal alkynes allows for the synthesis of fluorinated pyran scaffolds. Both cyclization processes can be performed under mild conditions allowing access to complex products rich in functionality. The cyclic systems are synthesized concisely (maximum four steps) from trifluoroethanol, an inexpensive fluorinated feedstock.

Introduction

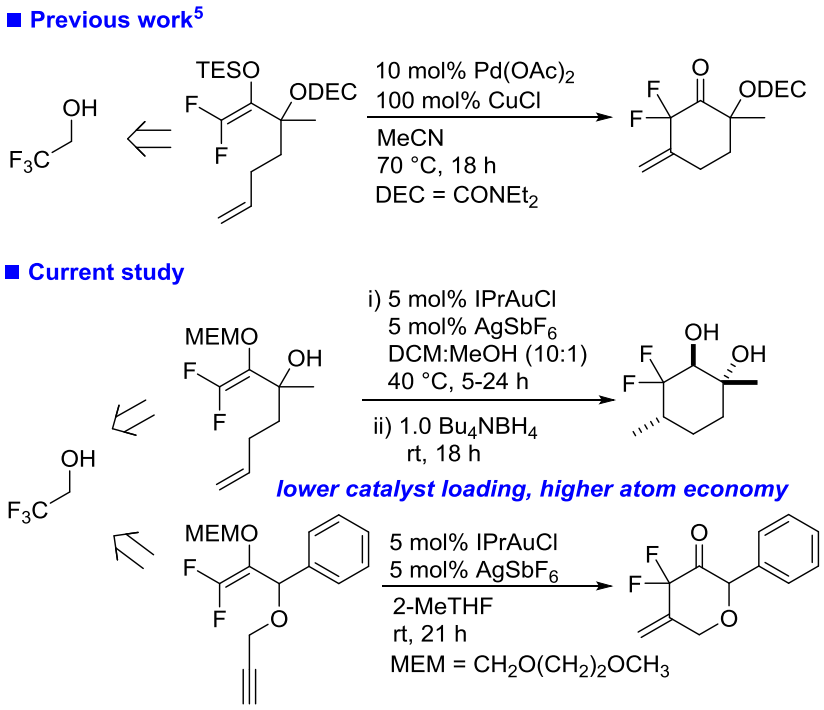
The design and synthesis of geminal difluoro compounds is an extremely important objective in medicinal chemistry owing to their unique biological properties, such as enzyme

inhibition, pKa modulation and improving metabolic stability.[1] However, efficient methods, starting from sustainable low cost starting materials, for the introduction of the *gem*-difluoromethylene group into cyclic molecules are still scarce. One of the most commonly implemented methods involves fluorination of a cyclic ketone with a nucleophilic fluorinating agent such as diethylaminosulfur trifluoride (DAST).[1b] An alternative method recently reported independently by the groups of Amii and Dilman utilizes a difluorocyclopropanation/ring expansion strategy to effectively introduce the $–CF_2$ moiety (**Scheme 1**).[2,3]



Scheme 1. Selection of methods for preparing difluorinated carbocycles.

Annulation chemistry based on difluorinated building blocks is much less well established.[4] In our efforts towards the development of new methods for the synthesis of selectively difluorinated carbocycles we recently reported the Saegusa-Ito cyclization as a concise and efficient protocol for the construction of selectively difluorinated cyclohexenones (**Scheme 2**).[5]

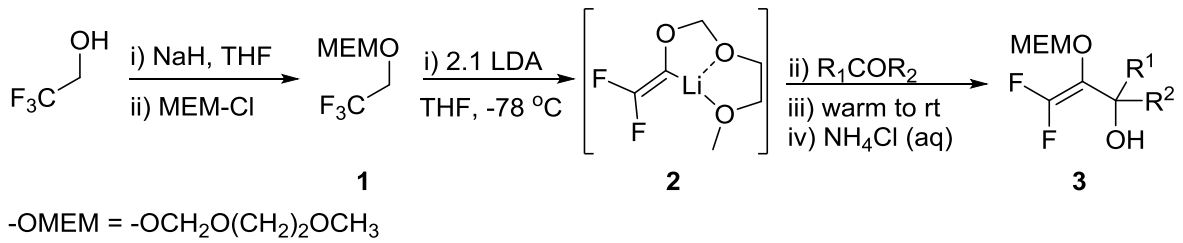


Scheme 2. Context of the current study.

Whilst this method represented a novel and exciting synthetic development, it is limited by poor atom economy arising from the use of two protecting groups, including the very robust carbamate. A more atom efficient cyclization based on difluorinated enol acetal nucleophiles would therefore be an attractive approach. While such species have proved effective substrates in sigmatropic rearrangements, their reactivity as nucleophiles has not been exploited in synthesis.[6] We envisioned that these species could be utilized in a divergent synthetic strategy to afford either difluorinated diols or pyrans through a gold(I) catalyzed cyclization (**Scheme 2**).[7]

Results and Discussion

Investigation into alkene cyclization. Following protection of trifluoroethanol, the requisite enol acetal species could be accessed from acetal **1** using our previously established one-pot dehydrofluorination/metalation procedure (**Scheme 3**).[8]

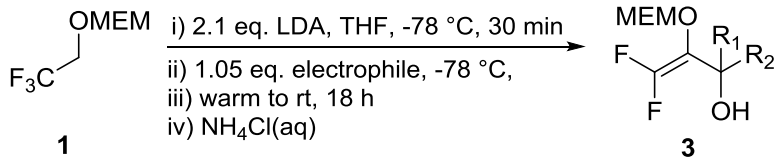


-OMEM = -$OCH_2O(CH_2)_2OCH_3$

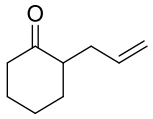
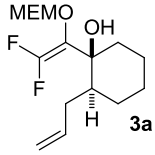
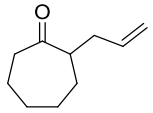
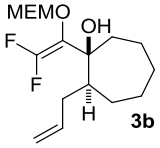
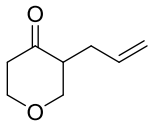
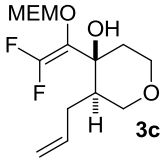
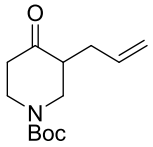
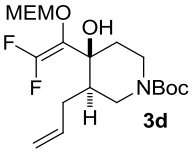
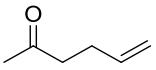
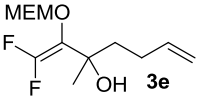
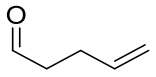
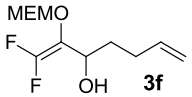
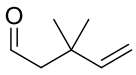
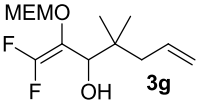
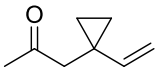
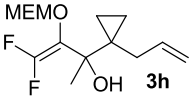
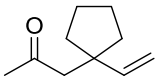
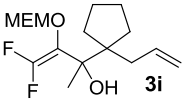
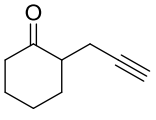
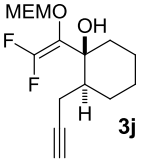
Scheme 3. Allylic alcohol synthesis

Treatment of **1** with lithium di*iso*propylamide generates the stabilized organolithium intermediate **2**. Addition of a γ,δ-unsaturated aldehyde or ketone followed by quenching with aqueous ammonium chloride delivers the desired allylic alcohols **3**. This procedure was typically performed on a > 10 mmol scale and, where possible, the products were purified by Kugelrohr distillation. A range of allylic alcohols were synthesized including, heterocyclic, geminally disubstituted and alicyclic analogues (**Table 1**).

Table 1: Difluorinated allylic alcohols **3** prepared from **1**.



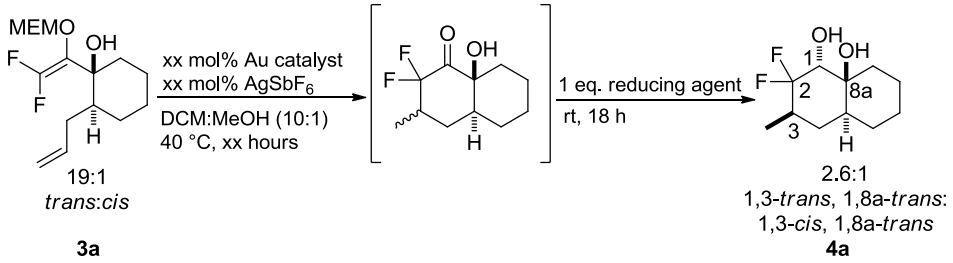
1 **3**

Electrophile	Product	Yield (%)[a]	dr[b]
	 **3a**	69[c]	19:1 *trans*-**3a**/*cis*-**3a**
	 **3b**	32[c, d]	32:1 *trans*-**3b**
	 **3c**	56[c]	3.5:1 *trans*-**3c**/*cis*-**3c**
	 **3d**	42[c, e]	4.9:1 *trans*-**3d**/*cis*-**3d**
	 **3e**	73	-
	 **3f**	64	-
	 **3g**	61[f]	-
	 **3h**	31[g]	-
	 **3i**	30[f]	-
	 **3j**	19[c, e]	32:1 *trans*-**3j**/*cis*-**3j**

[a] Isolated yields. All reactions were carried out with 12 mmol of **1** unless otherwise stated. [b] Diastereomeric ratio determined by ^{19}F NMR spectroscopy; for mixtures the major isomer is shown. [c] Isolated as a mixture of *cis*- and *trans*- diastereoisomers, major isomer shown. [d] At 9.5 mmol scale. [e] At 5 mmol scale. [f] At 10 mmol scale. [g] At 8 mmol scale.

These allylic alcohols were indefinitely stable when stored at 0 °C. With access to the requisite substrates secured, the allylic alcohol **3a** was chosen as a model substrate to investigate the proposed novel cyclization.[5] We began our studies using cyclization conditions similar to those reported by Toste for the carbocyclization of silyl enol ethers onto gold activated alkynes (**Table 2**).[9]

Table 2: Optimization of the one-pot cyclization reduction.



	Au cat.	Au cat. (mol%)	$AgSbF_6$ (mol%)	time (h)	reducing agent	yield (%)[a]
1	IPrAuCl	5	5	5	$NaBH_4$	42
2	IPrAuCl	5	5	5	TBAB	70
3	IPrAuCl	2.5	2.5	5	TBAB	68
4	IPrAuCl	1	1	22	TBAB	51
5	Ph_3PAuCl	5	5	-	-	0[b]
6	IPrAuCl	5	-	-	-	0[b]
7	None	-	5	-	-	0[b]

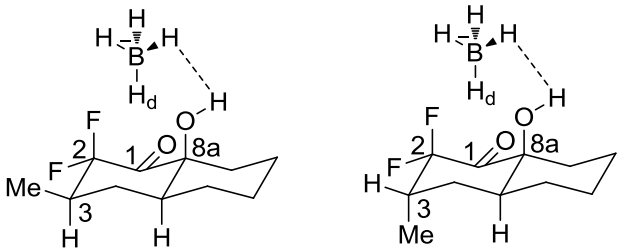
[a]Isolated Yield. Product was isolated as a mixture of 1,3-trans, 1,8a-trans and 1,3-cis, 1,8a-trans diastereoisomers (2.6:1), Major isomer shown. [b]No cyclized product could be detected by 19F NMR.

Using silver hexafluoroantimonate(V) as a chloride abstractor (generating the catalytically active cationic gold species *in situ*) in conjunction with 5 mol% 1,3-bis(2,6-di*iso*propylphenyl-imidazol-2-ylidene)gold(I) chloride (IPrAuCl)[10] ensured a successful

cyclization and the difluoroketone intermediate was reduced *in situ* using tetrabutylammonium borohydride (TBAB).

The improved solubility of TBAB over sodium borohydride in the reaction media may have accounted for the higher yield of **4a** (Entry 2, 70%, 2.6:1 dr).

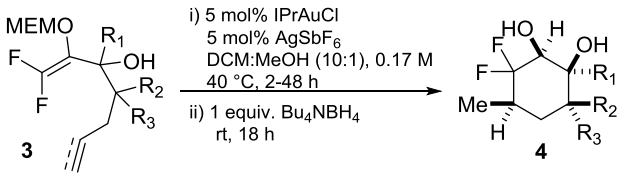
Lower catalyst loadings resulted in diminished yields and more protracted purification procedures, whilst application of a phosphine based catalyst yielded no cyclized product. The necessary control reactions in the absence of both silver and gold catalyst were also performed. In both cases no cyclized product could be detected from the reaction indicating that both silver and gold components must be present in order for the cyclization to proceed smoothly. It is possible that the α-hydroxy functionality may also provide some stereocontrol during the reduction process through dihydrogen bonding as no *cis*-diol was observed in the reaction mixture (**Scheme 4**).[11]

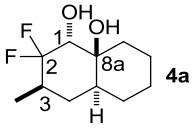
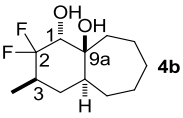
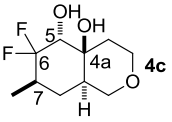
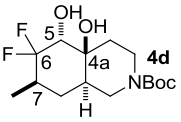
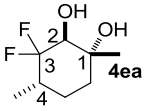
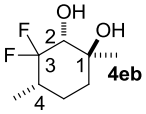
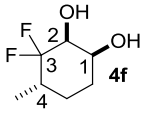
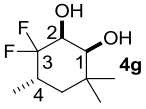
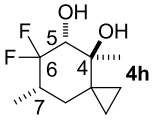
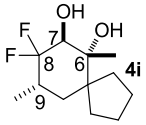


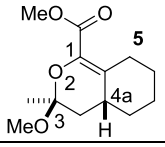
Scheme 4: Selective reduction affording 1,3-trans, 1,8a-trans **4a** (left) and 1,3-cis, 1,8a-trans **4a** (right).

With optimized conditions in hand, we next investigated the scope of the one pot cyclization/reduction reaction (**Table 3**).

Table 3: Scope of one-pot cyclization/reduction method.



	Allylic Alcohol	Product	Yield(%)[a]	dr[b]
1	19:1 *trans*-**3a**/*cis*-**3a**	 **4a**	70	**2.6:1** 1, 3-*trans*, 1, 8a-*trans*: 1, 3-*cis*, 1, 8a-*trans*
2	32:1 *trans*-**3b**/*cis*-**3b**	 **4b**	69	**4.9:1** 1, 3-*trans*, 1, 9a-*trans*: 1, 3-*cis*, 1, 9a-*trans*
3	3.5:1 *trans*-**3c**/*cis*-**3c**	 **4c**	48	**6.7:1.4:1** 4a, 5-*trans*, 5, 7-*trans*: 4a, 5-*trans*, 5, 7-*cis*: 4a, 5-*cis*, 5, 7-*cis*
4	4.9:1 *trans*-**3d**/*cis*-**3d**	 **4d**	50[c]	**3.4:0.9:1** 4a, 5-*trans*, 5, 7-*trans*: 4a, 5-*trans*, 5, 7-*cis*: 4a, 5-*cis*, 5, 7-*cis*
5	**3e**	 **4ea**	25[d]	**>20:1** 1, 2-*trans*, 2, 4-*trans*
6	**3e**	 **4eb**	16[d]	**>20:1** 1, 2-*trans*, 2, 4-*cis*
7	**3f**	 **4f**	11	**>20:1** 1, 2-*cis*, 2, 4-*trans*
8	**3g**	 **4g**	63	**>20:1** 1, 2-*cis*, 2, 4-*trans*
9	**3h**	 **4h**	29[d]	**1.3:1:0.1** 4, 5-*trans*, 5, 7-*cis*: 4, 5-*trans*, 5, 7-*trans*: 4, 5-*cis*, 5, 7-*cis*
10	**3i**	 **4i**	44	**3.8:1** 6, 7-*trans*, 7, 9-*trans*: 6, 7-*cis*, 7, 9-*trans*

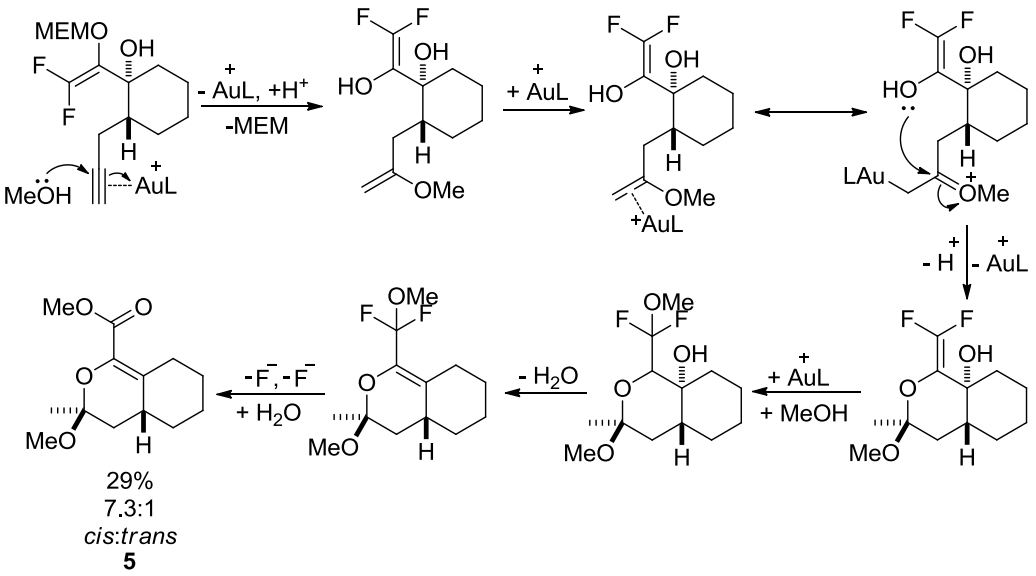
11	32:1 *trans*-**3j**/*cis*-**3j**		29[e]	**7.3:1** 3, 4a-*cis*: 3, 4a-*trans*

[a]Isolated yield. [b]Diastereomeric ratio determined by ^{19}F NMR spectroscopy; for mixtures the major isomer is shown. [c]10 days reaction time. [d]Diastereoisomers could be separated by normal phase chromatography. [e] From corresponding alkyne. 15 minutes reaction time and TBAB not added.

Cyclizations were typically performed on 1 mmol scale. Annelations afforded a range of fused bicyclic difluorinated diols **4a-4d** and the reaction also tolerated the formation of heterocycles **4c**-**4d**. More challenging annulations could also be performed on both unsubstituted and substituted cyclization precursors. It was possible to isolate the single *trans*, *trans* diastereoisomers of **4a** and **4b** by recrystallization of the mixtures by vapor diffusion using chloroform/pentane. We were able to isolate diastereoisomerically pure *trans*, *trans* **4ea** and *trans*, *cis* **4eb** as well as a mixture of both the *cis*,*cis* and *trans*, *trans* diastereoisomers (1.2:1 respectively, 15%) representing an overall yield of 56%. Annulations generally required a minimum level of substitution on the chain and a lower yield was obtained for the least substituted system **4f** (11 %). Gem-dimethyl **4g** was isolated in good yield and diastereoselectivity. In this case the selectivity of the reduction can be rationalized from consideration of the bulky borohydride reagent preferentially attacking the pro-equatorial face of the ketone, avoiding an unfavorable steric interaction with the axial C-3 methyl substituent of the ring.[12] Consequently, the carbon center which is reduced now bears an *S* configuration. Spirocycles **4h** and **4i** were both isolated as mixtures of diastereoisomers in moderate yield and for the spiro-cyclopropyl analogue, it was also possible to isolate small quantities of both *trans*, *trans* **4h** (5%) and *trans*, *cis* **4h** (6%) as single diastereoisomers (representing an overall yield of 40%). The stereochemical outcome of the reduction of spiro-cyclopentyl **4i** is equivalent to gem-dimethyl **4g** and the two diastereoisomers formed both have *S* configuration at the reduced carbon center. Conversely, the three diastereoisomers

isolated for **4h** have the opposite *R* configuration. This can be rationalized by consideration of the position of the 'axial' methylene group in **4h**. The strained cyclopropane ring requires bond angles to be smaller than those of typical sp^3 hybridized carbons; therefore, the methylene is not adopting a defined axial position, allowing the borohydride reagent to attack the pro-axial face of the ketone. The three-dimensional nature of such spirocyclic derivatives are of particular interest in medicinal chemistry and drug discovery.[13] In reactions where multiple diastereoisomers were formed there structures were elucidated through a combination of X-ray crystallographic analysis, 2D NMR and ^{19}F-^{1}H HOESY spectroscopic experiments.[14]

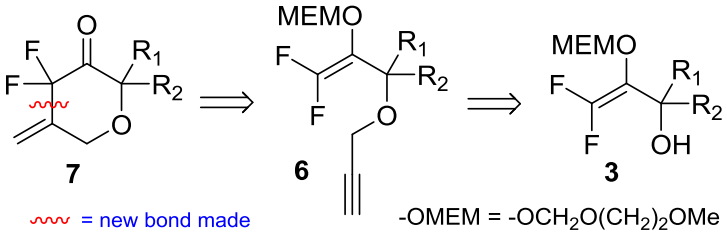
Attempted cyclization of a terminal alkyne substrate did not yield the desired product and instead afforded non-fluorinated pyran **5**. A working hypothesis as to how this product may be obtained is outlined in **Scheme 5**. We believe that initial attack of methanol onto the gold activated alkyne followed by a cyclization/elimination cascade is responsible for the formation of **5**.



Scheme 5. Proposed mechanism for formation of **5**.

Although unexpected this result was encouraging and we hypothesized that we could utilize the enhanced reactivity of the alkyne functionality to synthesize alternative difluorinated scaffolds.

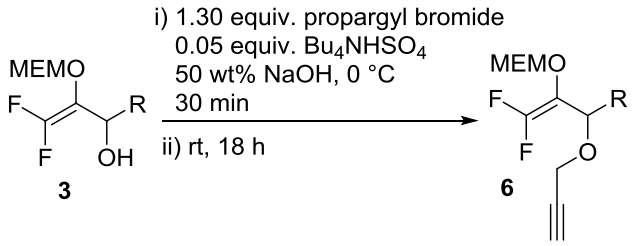
Investigation into alkyne cyclization. Pyrans are becoming an increasingly important heterocyclic scaffold in medicinal chemistry and can be found in a variety of bioactive compounds.[15] Only slight modification of the current synthetic route would enable access to structurally unique difluorinated pyran variants (**Scheme 6**)

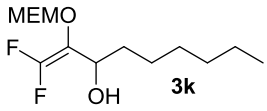
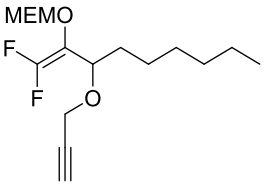
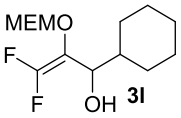
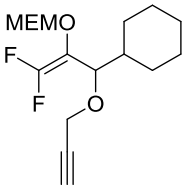
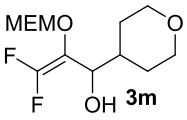
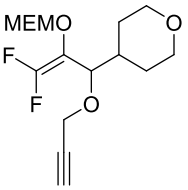
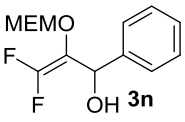
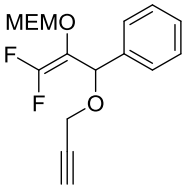
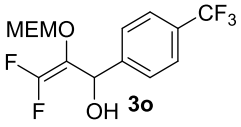
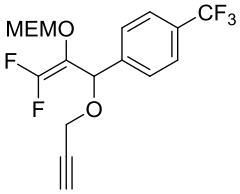
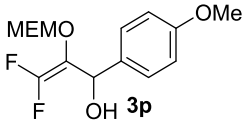
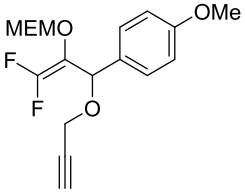


Scheme 6. Retrosynthetic route to difluorinated pyrans.

A small palette of propargyl ethers **6** were synthesized from difluoroallylic alcohols **3** using our published propargylation procedure (**Table 4**).[(6a)]

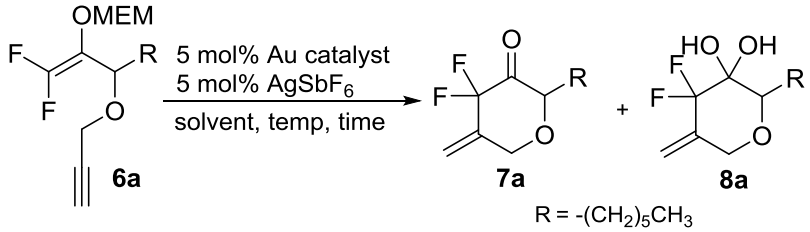
Table 4 – Propargyl ethers **6** synthesized from allylic alcohols **3**.



Allyl Alcohol	Propargyl Ether		Isolated Yield (%)
		**6a**	71
		**6b**	68
		**6c**	88
		**6d**	79
		**6e**	74
		**6f**	88

Simply treating difluoroallylic alcohols **3** with slight excess of propargyl bromide in a 50% aqueous solution of sodium hydroxide and a phase transfer catalyst afforded the desired propargyl ethers in good yield. Alkyne **6a** was chosen as a model substrate to investigate the proposed cyclization. Knowing that the alkyne moiety was susceptible to attack from methanol, the previously established cyclization conditions were employed in the absence of this solvent (**Table 5**).

Table 5: Optimisation of alkyne cyclization.



	Au catalyst	Temp (°C)	Solvent	Time (h)	Isolated Yield (%)[a]
1	IPrAuCl	rt	DCM	4	21
2	IPrAuCl	rt	Toluene	5	61
3	IPrAuCl	rt	THF	3	0[b]
4	IPrAuCl	rt	2-MeTHF	21	65
5	IPrAuCl	rt	CPME	5	61
6	IPrAuCl	40	2-MeTHF	2	49
7	Ph_3PAuCl	rt	2-MeTHF	24	54

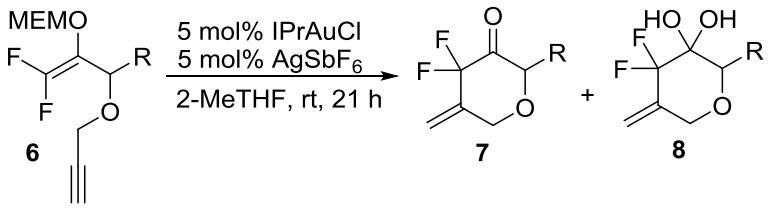
[a]Yield calculated based on the molecular weight of the hydrate component. [b] Polymerisation observed.

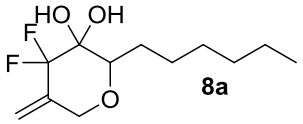
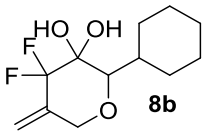
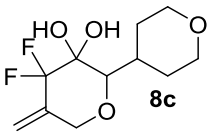
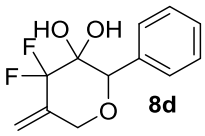
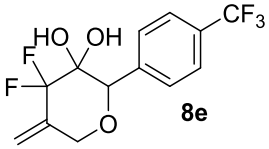
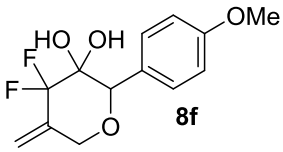
Using dichloromethane in a single solvent system it was possible to isolate the desired cyclized product, albeit in low yield. Given that α,α-difluoroketones are known to readily hydrate the products were often isolated as a mixture of the ketone **7a** and corresponding hydrate **8a**.[17] Upon switching to toluene the reaction was complete after 5 hours, and a significant increase in yield was observed. Whilst toluene appeared suitable for this particular substrate we found it to be incompatible with others and instead formed complex mixtures. As the objective was to identify a generic solvent which was not just substrate specific we decided to continue with further solvent screening. Polymerization of the reaction mixture

was observed when tetrahydrofuran was used. Tetrahydrofuran is known to undergo polymerization in the presence of catalytic quantities of metal halide salts, therefore the $AgSbF_6$ used in the reaction is likely to be the trigger for this process.[17] This unwanted polymerization could be avoided by switching to 2-methyltetrahydrofuran (2-MeTHF). Pleasingly, this solvent was not substrate specific and was compatible with other cyclizations. The ability to conduct the reaction in this inexpensive, sustainable solvent at room temperature is an attractive feature of the methodology.[18] Using cyclopentyl methyl ether (CPME) as an alternative ethereal solvent gave similar results to those obtained in toluene and also proved ineffective with other substrates screened. Following this screen we decided to use 2-MeTHF as the solvent of choice for moving forward with the investigation. Increasing the reaction temperature significantly decreased the reaction time; however, this was accompanied by a lower product yield. Ph_3PAuCl could also be used as a catalyst for the reaction; however, the best results were achieved by using IPrAuCl.

The reaction tolerated a variety of substituents. Carbocyclic analogue **8b** was isolated in comparable yield to the model substrate and, in this case, the ketone existed as the major component in the mixture. In contrast heterocycle **8c** was isolated exclusively as the hydrate. This material was recrystallized by vapor diffusion using tetrahydrofuran/pentane and its structure confirmed by single crystal X-ray diffraction. It was also pleasing to note that the reaction tolerated aromatic substituents. Phenyl analogue **8d** and electron withdrawing (trifluoromethyl) phenyl **8e** were isolated in good yield. This result was encouraging as we had previously been unable to access such cyclic difluorinated systems bearing aromatic substituents.[5] Electron withdrawing aromatic substituents were tolerated; however, we were unable to isolate electron rich aromatic **8f** and the reaction yielded only a complex mixture (**Table 6**).

Table 6 – Scope of Alkyne Cyclization.



	Alkyne	Product	Isolated Yield[a]	Ketone:Hydrate[b]
1	**6a**	 **8a**	65[c]	1:1
2	**6b**	 **8b**	63[d]	7.3:1
3	**6c**	 **8c**	62[c]	0:1
4	**6d**	 **8d**	52[c]	1:3.8
5	**6e**	 **8e**	52[c]	1:6.1
6	**6f**	 **8f**	0	-

[a]Isolated yield. Yield is based upon major component. [b]Ratio determined by ^{19}F NMR spectroscopy; in each example the hydrate component is shown. [c]Yield calculated based on the molecular weight of the hydrate component. [d]Yield calculated based on the molecular weight of the ketone component.

Conclusion

The methodology described allows for the concise synthesis of either difluorinated diol or difluorinated pyran scaffolds (3 steps and 4 steps respectively from trifluoroethanol, an

inexpensive commercial feedstock). Cyclizations are simple to perform and complex diol fragments can be synthesized *via* a one pot cyclization/reduction method under mild conditions in reactions vessels open to air. Alkyne cyclizations can be performed under similarly mild conditions at room temperature in 2-Methyltetrahydrofuran to afford products rich in functionality and sp^3 character and inaccessible by concise methods.

Experimental Section

General Methods. NMR spectra were recorded on Bruker DPX-400, AV-500 and Avance-II+ 600 spectrometers. ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded using the deuterated solvent as the lock and the residual solvent as the internal reference. The multiplicities of the spectroscopic data are presented in the following manner: s = singlet, d = doublet, dd = double doublet, dt = doublet of triplets, dq = doublet of quartets, dquint = doublet of quintets, ds = doublet of sextets, qd = quartet of doublets, qt = quartet of triplets, ddt = doublet of double triplets, ddd= doublet of doublet of doublets, dddd = doublet of double doublet of doublets, dddt = doublet of double doublet of triplets, tdd = triplet of doublet of doublets, td = triplet of doublets, t = triplet, q = quartet, m = multiplet and br. = broad. Unless stated otherwise, all couplings refer to ^{3}J homocouplings. IR spectra were recorded on an ATR IR spectrometer. GC/MS spectra were obtained on an instrument fitted with a DB5-type column (30 m × 0.25 μm) running a 40−320 °C temperature program, ramp rate 20 °C min $^{-1}$ with helium carrier gas flow at 1 cm^3 min^{-1}. Chemical ionisation (CI) (methane/ammonia) and Electron Ionisation (EI) mass spectra were recorded on either an Agilent Technologies 5975C mass spectrometer or a FINNIGAN MAT 95 high resolution double focussing (BE) mass spectrometer (EPSRC National Mass Spectrometry Service Centre, Swansea). HRMS measurements were obtained from a Waters GCT Premier MS (CI), Finnigan Mat 95 XP (EI-MS and/or APCI-MS), Thermo Scientific LTQ Orbitrap XL via Advion TriVersa NanoMate infusion (ESI) or Waters Xevo G2-S Atmospheric Solids Analysis Probe (APCI, Positive

mode, Xevo) spectrometers (EPSRC National Mass Spectrometry Service Centre, Swansea). Thin layer chromatography was performed on pre-coated aluminium-backed silica gel plates (E. Merck AG, Darmstadt, Germany. Silica gel 60 F254, thickness 0.2 mm). Visualisation was achieved using potassium permanganate dip or UV detection at 254 nm. Column chromatography was performed on silica gel (Zeochem, Zeoprep 60 HYD, 40-63 μm) using a Büchi Sepacore system. Hexane was distilled before chromatography. [(IPr)AuCl] (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene, 95%) and $AgSbF_6$ (98%) were purchased from Strem Chemicals and used as received. THF was dried using a PureSolv system from Innovative Technology, Inc.. Diisopropylamine was distilled from 4Å molecular sieves (30 °C/140 mbar) and stored under nitrogen over 4Å molecular sieves. All other chemicals were purchased from Sigma Aldrich, Alfa Aesar, or Fluorochem. All compounds were named according to the ChemDraw Professional 15.0 package and checked against Scifinder® chemical database. Single-crystal data were measured at with Oxford Diffraction CCD Diffractometers and with sealed-tube generated, graphite monochromated radiation. The exception was **7c** for which data was measured by the UK National Crysallography Service using a Rigaku FRE+ rotating anode.[19] The structures were solved by direct methods (SIR92, SHELXS) and refined to convergence on F^2 and against all independent reflections by full-matrix least-squares using SHELXL programs.[20,21] All non-hydrogen atoms were refined anisotropically and hydrogen atoms were geometrically placed and allowed to ride on their parent atoms. For compound *trans*, *trans*-**4a**, crystals grew as stacked plates. Reprocessing the raw data for this compound as a twinned sample gave a hklf 5 format reflection file. Refinement with this gave significantly better R factors and residual electron density features with BASF = 0.265(23). Table S1 contains selected crystallographic and refinement data. CCDC-1582563 to CCDC-1582570 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data

Centre via www.ccdc.cam.ac.uk/data_request/cif. LDA and *n*-Butyllithium (2.5 M solution in hexanes) was titrated according to the method of Duhamel and Plaquevent.[22] The data for products **3f**, **3g**, **3n**, and **3p** have previously been reported.[6c,8,23]

General Procedure A: Allylic Alcohol Preparation. Trans-2-allyl-1-(2,2-difluoro-1 ((2-methoxyethoxy)methoxy)ethenyl) cyclohexan-1-ol (trans-**3a**) and cis-2-allyl-1-(2,2-difluoro-1' ((2-methoxyethoxy)methoxy)ethenyl) cyclohexan-1-ol (cis-**3a**). Prepared according to the method of Percy and co-workers.[8] n-Butyllithium (12.9 mL of a 1.94 M solution in hexanes, 25 mmol) was added dropwise to a solution of diisopropylamine (3.70 mL, 26 mmol) in THF (12 mL) at -78 °C. Following addition the reaction vessel was transferred to an ice bath and allowed to warm to 0 °C and stirred at this temperature for 45 minutes. The flask was then re-cooled to -78 °C and acetal **1**[8] (1.90 mL, 12 mmol) was added dropwise over 15 minutes. The dark orange suspension was stirred at -78 °C for 30 minutes, then allylcyclohexanone (1.97 mL, 13.2 mmol) was added. The reaction mixture was allowed to warm to rt overnight; the reaction mixture turned homogeneous and darkened over this time. The mixture was quenched with saturated aqueous ammonium chloride (30 mL) and extracted with ethyl acetate (4 x 60mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated to afford crude allylic alcohols trans-**3a** and cis-**3a** (3.23 g) as a dark brown oil. The material was taken up in dichloromethane and transferred by pipette to a glass sinter funnel (diameter 7.5 cm) containing a pad of silica (54 g). The product was then eluted from the plug with 70% diethyl ether/hexane (600 mL). The solvent was evaporated under reduced pressure to afford the product as a pale orange oil (2.93 g). The crude allylic alcohol was purified by Kugelrohr distillation to afford an inseparable mixture of trans-**3a** and cis-**3a** as a pale yellow oil (2.53 g, 69 %, 95:5). b.p. = 97 °C / 0.04 mmHg; R_f = 0.27 (40 % diethyl ether in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.77 (dddd, J = 17.0, 10.1, 8.5, 5.8 Hz, 1H), 5.06-4.95 (m, 2H), 4.93 (app. s, 2H), 3.94-3.81 (m, 2H), 3.62-3.54 (m, 2H), 3.40 (s, 3H), 2.62

(br. s, 1H), 2.29-2.16 (m, 1H), 1.98-1.88 (m, 1H), 1.86-1.08 (envelope, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.4 (t, $^1J_{C\text{-}F}$ = 287.1 Hz), 137.6, 121.5 (dd, $^2J_{C\text{-}F}$ = 33.1, 10.3 Hz), 115.8, 98.7 (t, $^4J_{C\text{-}F}$ = 4.2 Hz), 73.7 (d, $^3J_{C\text{-}F}$ = 5.6 Hz), 71.6, 68.9, 58.9, 41.9 (d, $^4J_{C\text{-}F}$ = 4.8 Hz), 37.1 (t, $^4J_{C\text{-}F}$ = 2.9 Hz), 35.2, 26.4, 25.3, 21.2 ppm; Major trans-diastereoisomer **3a** (assigned on the basis of δ and intensity) ^{19}F NMR (376 MHz, $CDCl_3$): δ = -98.8 (d, ^2J = 73.4 Hz, 1F), -103.6 (d, ^2J = 73.4 Hz, 1F) ppm;* Minor cis-diastereoisomer **3a** (assigned on the basis of δ and intensity) ^{19}F NMR (376 MHz, $CDCl_3$): δ = -97.5 (d, ^2J = 68.6 Hz, 1F), 104.4 (d, ^2J = 68.6 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3450, 2934, 1738, 1450, 1104, 1059 cm^{-1}; HRMS (NSI): calcd for $C_{15}H_{28}F_2O_4N$, 324.1981 $[M+NH_4]^+$, found: 324.1983; MS (CI): m/z (%): 201 (14) $[M\text{-}C_4H_9O_3]^+$, 89 (100) $[C_4H_9O_2]^+$, 59 (85) $[C_3H_7O]^+$; t_R (GC) = 13.17 minutes**. *this is by comparison with compounds from the Saegusa-Ito series.[5] ** the cis- and trans-stereoisomers appeared as one peak by GC.

trans-2-allyl-1-(2,2-difluoro-1-((2-methoxyethoxy)methoxy)vinyl)cycloheptan-1-ol (trans-**3b**) and cis-2-allyl-1-(2,2-difluoro-1-((2-methoxyethoxy)methoxy)vinyl)cycloheptan-1-ol (cis-**3b**). Prepared as for trans-**3a** and cis-**3a** from acetal (1.50 mL, 9 mmol), n-butyllithium (12.8 mL of a 1.48 M solution in hexanes, 19 mmol), diisopropylamine (2.85 mL, 20 mmol) and allylcycloheptanone[5] (1.45 g, 9.5 mmol) in THF (12 mL). The crude allylic alcohol (3.13 g) was purified by Kugelrohr distillation to afford an inseparable mixture of trans-**3b** and cis-**3b** as a pale yellow oil (0.99 g, 32 %, 97:3). b.p. = 93 °C / 0.04 mmHg; R_f = 0.27 (40 % diethyl ether in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.79 (dddd, J = 16.9, 10.2, 8.6, 5.2 Hz, 1H), 5.08-4.98 (m, 2H), 4.96, 4.92 (ABq, J_{AB} = 6.1 Hz, 2H), 3.94-3.84 (m, 2H), 3.62-3.52 (m, 2H), 3.40 (s, 3H), 2.79 (br. s, 1H), 2.27-2.15 (m, 1H), 2.09-1.99 (m, 1H), 1.99-1.89 (m, 1H), 1.87-1.20 (envelope, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.1 (t, $^1J_{C\text{-}F}$ = 287.5 Hz), 137.6, 121.9 (dd, $^2J_{C\text{-}F}$ = 32.2, 10.2 Hz), 115.5, 98.3 (t, $^4J_{C\text{-}F}$ = 4.2 Hz), 76.3 (d, $^3J_{C\text{-}F}$ = 6.0 Hz), 71.1, 68.5, 58.5, 45.1 (d, $^4J_{C\text{-}F}$ = 5.2 Hz), 39.4, 35.8, 27.7, 26.8, 24.9,

20.0 ppm; Major trans-diastereoisomer **3b** (assigned on the basis of δ and intensity) ^{19}F NMR (376 MHz, $CDCl_3$): δ = -98.6 (d, ^{2}J = 74.1 Hz, 1F), -103.9 (d, ^{2}J = 74.1 Hz, 1F) ppm;* Minor cis-diastereoisomer **3b** (assigned on the basis of δ and intensity) ^{19}F NMR (376 MHz, $CDCl_3$): δ = -97.7 (d, ^{2}J = 72.6 Hz, 1F), 103.0 (d, ^{2}J = 72.6 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3464, 2921, 1733, 1262, 1050, 952 cm^{-1}; HRMS (APCI): calcd for $C_{16}H_{30}F_2O_4N_1$, 338.2137 $[M+NH_4]^+$, found: 338.2140; MS (CI): m/z (%): 338 (100) $[M+NH_4]^+$; t_R (GC) = 14.17 minutes.** *this is by comparison with compounds from the Saegusa-Ito series.[5] ** the cis- and trans-stereoisomers appeared as one peak by GC.

*trans-3-allyl-4-(2,2-difluoro-1-((2-methoxyethoxy)methoxy)vinyl)tetrahydro-2H-pyran-4-ol (trans-**3c**) and cis-3-allyl-4-(2,2-difluoro-1-((2-methoxyethoxy)methoxy)vinyl)tetrahydro-2H-pyran-4-ol (cis-**3c**)*. Prepared as for *trans*-**3a** and *cis*-**3a** from acetal (1.90 mL, 12 mmol), *n*-butyllithium (12.9 mL of a 1.94 M solution in hexanes, 25 mmol), di*iso*propylamine (3.70 mL, 26 mmol) and 2-allyltetrahydropyranone[5] (1.68 g, 12 mmol) in THF (12 mL). The crude allylic alcohol (3.13 g) was purified by Kugelrohr distillation to afford an inseparable mixture of *trans*-**3c** and *cis*-**3c** as a pale yellow oil (2.06 g, 56 %, 78:22). b.p. = 93 °C / 0.04 mmHg; R_f= 0.25 (30 % ethyl acetate in hexane); Major *trans*-diastereoisomer **3c** (assigned on the basis of δ and intensity) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.90-5.65 (m, 1H), 5.21-4.81 (m, including 4.96 (app. s, 2H) 2H), 4.03-3.67 (envelope, 5H), 3.60 (t, *J* = 4.7 Hz, 2H), 3.57-3.49 (m, 1H), 3.41 (s, 3H), 3.16 (br. s, 1H), 2.29-1.39 (envelope, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.9 (t, $^1J_{C\text{-}F}$ = 288.1 Hz), 135.8, 120.5 (dd, $^2J_{C\text{-}F}$ = 32.8, 10.4 Hz), 115.9, 98.6 (t, $^4J_{C\text{-}F}$ = 4.4 Hz), 71.0, 70.5 (d, $^3J_{C\text{-}F}$ = 5.7 Hz), 68.6, 66.7, 62.9, 58.4, 40.5 (d, $^4J_{C\text{-}F}$ = 5.1 Hz), 36.6, 30.4 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -98.0 (d, ^2J = 71.8 Hz, 1F), -103.3 (d, ^2J = 71.8 Hz, 1F) ppm;* Minor *cis*-diastereoisomer **3c** (assigned on the basis of δ and intensity) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.41 (s, OCH_3, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0 (t, $^1J_{C\text{-}F}$ = 290.7 Hz), 136.4,

121.4 (dd, $^{2}J_{C\text{-}F}$ = 31.2, 12.0 Hz), 116.0, 70.9, 68.2, 63.6, 62.5 (d, $^{3}J_{C\text{-}F}$ = 4.8 Hz), 41.7, 40.0, 31.7 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -96.7 (d, ^{2}J = 66.4 Hz, 1F), 104.5 (dt, ^{2}J = 68.6, $^{5}J_{F\text{-}H}$ = 4.9 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3443, 2928, 1736, 1100, 1056 cm^{-1}; HRMS (APCI): calcd for $C_{14}H_{26}F_2O_5N$, 326.1774 $[M+NH_4]^+$, found: 326.1772; MS (CI): *m/z* (%): 326 (100) $[M+NH_4]^+$; t_R (GC) = 13.73 minutes (major *trans*-diastereoisomer), 13.66 minutes (minor *cis*-diastereoisomer). *this is by comparison with compounds from the Saegusa-Ito series.[5]

*trans-tert-butyl -3-allyl-4-(2,2-difluoro-1-((2-methoxyethoxy)methoxy)vinyl)-4-hydroxypiperidine-1-carboxylate (trans-**3d**) and cis-tert-butyl -3-allyl-4-(2,2-difluoro-1-((2-methoxyethoxy)methoxy)vinyl)-4-hydroxypiperidine-1-carboxylate (cis-**3d**)*. Prepared as for *trans*-**3a** and *cis*-**3a** from acetal (0.79 mL, 5mmol), commercial LDA (5.9 mL of a 1.70 M solution in THF/heptane/ethylbenzene, 24 mmol) and *tert*-butyl 3-allyl-4-oxopiperidine-1-carboxylate[5] (1.19 g, 5 mmol) in THF (5 mL). The crude allylic alcohol was purified by flash column chromatography (90 g cartridge, 45% ethyl acetate in hexane) to afford an inseparable mixture of *trans*-**3d** and *cis*-**3d** as a pale orange oil (0.86 g, 42 %, 83:17). R_f = 0.59 (50 % ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.79 (dddd, *J* = 17.3, 10.1, 8.5, 5.7 Hz, 1H), 5.14-4.99 (m, 2H), 4.94 (s, 2H), 4.17-3.71 (m, 4H), 3.70-3.51 (m, 2H), 3.41 (s, 3H), 3.31-3.04 (m, 2H), 2.87 (br. s, 1H), 2.34-2.18 (m, 1H), 2.06-1.73 (m, 4H), 1.47 (s, 9H) ppm (the ^{1}H NMR gave a clear well resolved spectrum at RT and did not require heating). Major *trans*-diastereoisomer **3d** (assigned on the basis of δ and intensity) ^{13}C NMR (150 MHz, toluene-d_8, 373 K): δ = 154.7 (t, $^{1}J_{C\text{-}F}$ = 288.1 Hz), 154.2, 137.0, 121.2 (dd, $^{2}J_{C\text{-}F}$ = 32.4. 10.7 Hz), 115.5, 98.8 (dd, $^{4}J_{C\text{-}F}$ = 5.8, 3.4 Hz), 78.4, 72.1 (d, $^{3}J_{C\text{-}F}$ = 5.2 Hz), 71.5, 69.0, 58.0, 44.0, 41.3 (d, $^{4}J_{C\text{-}F}$ = 4.2 Hz), 39.6, 36.5 (t, $^{4}J_{C\text{-}F}$ = 3.2 Hz), 31.9, 28.1 ppm; ^{19}F (376 MHz, toluene-d_8, 373 K): δ = -98.6 (d, ^{2}J = 74.3 Hz, 1F), -104.6 (d, ^{2}J = 74.3 Hz, 1F) ppm;* Minor *cis*-diastereoisomer **3d** (assigned on the basis of δ and intensity) ^{13}C NMR (150 MHz, toluene-d_8, 373 K): δ = 155.7 (t, $^{1}J_{C\text{-}F}$ = 289.3 Hz), 154.6, 136.4, 115.8, 78.3, 72.4 (dd,

$^{3}J_{C\text{-}F}$ = 4.6, 2.3 Hz), 71.4, 68.8, 50.1, 42.9, 40.9, 39.7, 32.1, 28.1 ppm; ^{19}F (376 MHz, toluene-d_8, 373 K): δ = -97.5 (d, ^{2}J = 69.1 Hz, 1F), -104.8 (d, ^{2}J = 69.1 Hz, 1F) ppm; ν̄/(neat) = 3430, 2926, 1736, 1666, 1426, 1158, 1056, 989 cm^{-1}; HRMS (NSI-ES): calcd for $C_{19}H_{32}F_2NO_6$, 408.2192 $[M+H]^+$, found: 408.2189; MS (CI): *m/z* (%): 408 (100) $[M+H]^+$; t_R (GC) = 14.91 minutes.** *this is by comparison with compounds from the Saegusa-Ito series.[5] ** the *cis*- and *trans*-stereoisomers appeared as one peak by GC.

1,1-difluoro-2-((2-methoxyethoxy)methoxy)-3-methylhepta-1,6-dien-3-ol ***(3e)***. Prepared as for *trans*-**3a** and *cis*-**3a** from acetal (1.90 mL, 12 mmol), *n*-butyllithium (12.9 mL of a 1.94 M solution in hexanes, 25 mmol), di*iso*propylamine (3.70 mL, 26 mmol) and 5-hexen-2-one (1.39 mL, 12 mmol) in THF (12 mL). The crude product (2.54 g) was purified by Kugelrohr distillation to afford **3e** (2.33 g, 73 %) as a pale yellow oil. b.p. = 78 °C / 0.04 mmHg; R_f = 0.27 (50 % diethyl ether in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.85 (ddt, J = 16.9, 10.1, 6.5 Hz, 1H), 5.06 (dq, J = 16.9, ^{4}J = ^{2}J = 1.9 Hz, 1H), 5.00 (d, ^{2}J = 6.4 Hz, 1H), 4.97 (dq, J = 10.1, ^{4}J = ^{2}J = 1.9 Hz, 1H), 4.93 (d, ^{2}J = 6.4 Hz, 1H), 3.98-3.81 (m, 2H), 3.59 (br. t, J = 4.8 Hz, 2H), 3.41 (s, 3H), 3.39 (br. s, 1H), 2.10 (app. qt, J = 7.6, ^{4}J = 1.9 Hz, 2H), 1.87-1.68 (m, 2H), 1.42 (d, $^{5}J_{H\text{-}F}$ = 4.8 Hz, 3H) ppm; ^{13}C (100 MHz, $CDCl_3$): δ = 154.2 (t, $^{1}J_{C\text{-}F}$ = 288.6 Hz), 137.8, 121.0 (dd, $^{2}J_{C\text{-}F}$ = 32.7, 10.5 Hz), 114.0, 98.5 (t, $^{4}J_{C\text{-}F}$ = 4.1 Hz), 71.1 (d, $^{3}J_{C\text{-}F}$ = 3.7 Hz), 71.0, 68.5, 58.5, 39.3, 28.1, 24.5 (d, $^{4}J_{C\text{-}F}$ = 7.1 Hz) ppm; ^{19}F (376 MHz, $CDCl_3$): δ = -98.4 (d, ^{2}J = 70.9 Hz, 1F), -103.9 (app. dq, ^{2}J = 70.9 Hz, $^{5}J_{F\text{-}H}$ = 4.8 Hz, 1F) ppm; ν̄/(neat) = 3447, 2928, 1736, 1102, 1024 cm^{-1}; HRMS (NSI-ES): calcd for $C_{12}H_{20}F_2O_4Na$, 289.1222 $[M+Na]^+$, found: 289.1221; MS (CI): *m/z* (%): 161 (4) $[M-C_4H_9O_3]^+$, 89 (73) $[C_4H_9O_2]^+$, 59 (100) $[C_3H_7O]^+$; t_R (GC) = 11.38 minutes.

1,1-Difluoro-2-((methoxyethoxy)methoxy)-3-methyl-4-cyclopropyl-hepta-1,6-dien-3-ol ***(3h)***. Prepared as for *trans*-**3a** and *cis*-**3a** from acetal (1.26 mL, 8 mmol), *n*-butyllithium (8.3

mL of a 1.98 M solution in hexanes, 16 mmol), di*iso*propylamine (2.38 mL, 17 mmol) and 1-(1-allylcyclopropyl)ethan-1-one[5] (1.00 g, 8 mmol) in THF (8 mL). The crude product (1.41 g) was purified by Kugelrohr distillation to afford **3h** (0.730 g, 31 %) as a pale yellow oil. b.p. = 93 °C / 0.06 mmHg; R_f = 0.54 (40 % ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.70 (ddt, *J* = 17.3, 10.2, 7.3 Hz, 1H), 5.11-4.96 (m, including 5.05 (d, ^2J = 6.4 Hz, 1H), 2H), 4.91 (d, ^2J = 6.4 Hz, 1H), 4.00-3.80 (m, 2H), 3.59 (t, *J* = 4.8 Hz, 2H), 3.41 (s, 3H), 3.12 (br. s, 1H), 2.34-2.13 (m, 2H), 1.42 (d, $^5J_{H\text{-}F}$ = 5.8 Hz, 3H), 0.84-0.75 (m, 1H), 0.63 (ddd, ^2J = 9.9, *J* = 5.8, 4.3 Hz, 1H) 0.45-0.35 (m, 1H), 0.29 (ddd, ^2J = 9.9, *J* = 5.5, 4.3 Hz, 1H) ppm; ^{13}C (100 MHz, $CDCl_3$): δ = 154.6 (t, $^1J_{C\text{-}F}$ = 288.8 Hz), 135.6, 120.3 (dd, $^2J_{C\text{-}F}$ = 32.6, 11.5 Hz), 116.0, 98.4 (t, $^4J_{C\text{-}F}$ = 4.2 Hz), 72.1 (d, $^3J_{C\text{-}F}$ = 6.3 Hz), 71.1, 68.6, 58.5, 37.1, 25.6, 22.9 (d, $^4J_{C\text{-}F}$ = 8.5 Hz), 7.0, 5.1 ppm; ^{19}F (376 MHz, $CDCl_3$): δ = -97.7 (d, ^2J = 68.4 Hz, 1F), -102.7 (dq, ^2J = 68.4 Hz, $^5J_{F\text{-}H}$ = 5.8 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3465, 2887, 1736, 1022, 937 cm^{-1}; HRMS (ESI): calcd for $C_{14}H_{26}F_2O_4N$, 310.1824 $[M+NH_4]^+$, found: 310.1826; MS (EI): *m/z* (%): 161 (2) $[M\text{-}C_6H_9F_2O_3]^+$, 89 (69) $[C_4H_9O_2]^+$, 59 (100) $[C_3H_7O]^+$; t_R (GC) = 12.75 minutes.

*1,1-Difluoro-2-((methoxyethoxy)methoxy)-3-methyl-4-cyclopentyl-hepta-1,6-dien-3-ol (**3i**)*. Prepared as for *trans*-**3a** and *cis*-**3a** from acetal (1.58 mL, 10 mmol), *n*-butyllithium (9.8 mL of a 2.04 M solution in hexanes, 20 mmol), di*iso*propylamine (3.38 mL, 24 mmol) and 1-(1-allylcyclopentyl)ethan-1-one[5] (1.52 g, 10 mmol) in THF (11 mL). The crude product (2.13 g) was purified by Kugelrohr distillation to afford **3i** (0.965 g, 30%) as a pale yellow oil. b.p. = 100 °C / 0.04 mmHg; R_f = 0.30 (40 % diethyl ether in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.70 (ddt, *J* = 17.3, 10.1, 7.3 Hz, 1H), 5.11-4.99 (m, including 5.04 (d, ^2J = 6.3 Hz, 1H), 2H), 4.88 (dt, ^2J = 6.4, $^5J_{H\text{-}F}$ = 1 Hz, 1H), 3.94-3.80 (m, 2H), 3.58 (t, *J* = 4.8 Hz, 2H), 3.40 (s, 3H), 3.12 (br. s, 1H), 2.19 (d, *J* = 7.3 Hz, 2H), 1.88-1.74 (m, 2H), 1.68-1.35 (m, including 1.41 (d, $^5J_{H\text{-}F}$ = 5.4 Hz, 3H), 6H) ppm; ^{13}C (100 MHz, $CDCl_3$): δ = 155.0 (t, $^1J_{C\text{-}F}$ =

288.3 Hz), 136.2, 120.3 (dd, $^{2}J_{C\text{-}F}$ = 32.1, 11.3 Hz), 116.3, 99.0 (t, $^{4}J_{C\text{-}F}$ = 4.7 Hz), 75.9 (d, $^{3}J_{C\text{-}F}$ = 4.8 Hz), 71.1, 68.9, 58.5, 54.1, 41.1, 32.1, 31.6, 25.9, 25.2, 22.3 (d, $^{4}J_{C\text{-}F}$ = 8.6 Hz) ppm; ^{19}F (376 MHz, $CDCl_3$): δ = -97.7 (d, ^{2}J = 71.0 Hz, 1F), -101.33 (dq, ^{2}J = 71.0 Hz, $^{5}J_{F\text{-}H}$ = 5.4 Hz, 1F) ppm; the 1.0 Hz $^{5}J_{H\text{-}F}$ = splitting could not be resolved in the 376 MHz ^{19}F NMR spectrum; $\bar{\nu}$/(neat) = 3494, 2944, 1731, 1266, 1065, 909 cm^{-1}; HRMS (APCI): calcd for $C_{16}H_{30}F_2O_4N$, 338.2137 $[M+NH_4]^+$, found: 338.2143; MS (CI): *m/z* (%): 338 (100) $[M+NH_4]^+$; t_R (GC) = 13.78 minutes.

*Trans-1-(2,2-difluoro-1-((2-methoxyethoxy)methoxy)vinyl)-2-(prop-2-yn-1-yl)cyclohexan-1-ol (trans-**3j**) and cis-1-(2,2-difluoro-1-((2-methoxyethoxy)methoxy)vinyl)-2-(prop-2-yn-1-yl)cyclohexan-1-ol (cis-**3j**)*. Prepared as for *trans*-**3a** and *cis*-**3a** from acetal (0.79 mL, 5 mmol), *n*-butyllithium (5.4 mL of a 1.84 M solution in hexanes, 10 mmol), di*iso*propylamine (1.69 mL, 12 mmol) and 2-(prop-2-ynyl)cyclohexanone[23] (0.68 g, 5 mmol) in THF (5 mL). The crude allylic alcohol was purified by flash column chromatography using a Thompson Single Step cartridge (90 g cartridge, 20 % ethyl acetate in hexane) to afford an inseparable mixture of *trans*-**3j** and *cis*-**3j** as a pale orange oil (0.291 g, 19 %, 97:3). R_f = 0.82 (50 % ethyl acetate in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.94 (app. s, 2H), 3.94-3.81 (m, 2H), 3.59 (app. t, *J* = 4.8 Hz, 2H), 3.41 (s, 3H), 2.93 (s, 1H), 2.34 (dt, ^{2}J = 16.9, *J* = ^{4}J = 2.8 Hz, 1H), 2.20 (ddd, ^{2}J = 16.9, *J* = 8.9, ^{4}J = 2.8 Hz, 1H), 1.99 (t, ^{4}J = 2.8 Hz, 1H), 1.94-1.47 (envelope, 8H), 1.36-1.21 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.0 (t, $^{1}J_{C\text{-}F}$ = 289.2 Hz), 120.8 (dd, $^{2}J_{C\text{-}F}$ = 32.9. 10.0 Hz), 98.3 (t, $^{4}J_{C\text{-}F}$ = 4.5 Hz), 83.3, 72.6 (d, $^{3}J_{C\text{-}F}$ = 5.6 Hz), 71.1, 68.8, 68.5, 58.5, 41.1 (d, $^{4}J_{C\text{-}F}$ = 4.7 Hz), 36.4 (t, $^{4}J_{C\text{-}F}$ = 3.1 Hz), 26.1, 24.7, 20.6, 19.7 ppm; Major *trans*-diastereoisomer **3j** (assigned on the basis of δ and intensity) ^{19}F (376 MHz, $CDCl_3$): δ = -98.0 (d, ^{2}J = 72.3 Hz, 1F), -103.1 (d, ^{2}J = 72.3 Hz, 1F) ppm;* Minor *cis*-diastereoisomer **3j** (assigned on the basis of δ and intensity ^{19}F (376 MHz, $CDCl_3$): δ = -96.7 (d, ^{2}J = 67.2 Hz, 1F), -103.7 (d, ^{2}J = 67.2 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3452, 3302, 2928, 1734, 1216, 1056 cm^{-1};

HRMS (ESI): calcd for $C_{15}H_{23}F_2O_4$, 305.1564 $[M+H]^+$, found: 305.1557; MS (CI): *m/z* (%): 305 (10) $[M+H]^+$, 322 (15) $[M+NH_4]^+$; t_R (GC) = 12.90 minutes.** *this is by comparison with compounds from the Saegusa-Ito series.[5] ** the *cis*- and *trans*-stereoisomers appeared as one peak by GC.

*1,1-difluoro-2-((2-methoxyethoxy)methoxy)non-1-en-3-ol (**3k**)*. Prepared as for *trans*-**3a** and *cis*-**3a** from acetal (1.90 mL, 12 mmol), *n*-butyllithium (12.9 mL of a 1.94 M solution in hexanes, 25 mmol), di*iso*propylamine (3.70 mL, 26 mmol) and heptanal (1.37 g, 12 mmol) in THF (12 mL). The crude allylic alcohol (2.63 g) was purified by Kugelrohr distillation to afford **3k** as a pale yellow oil (2.20 g, 65 %). b.p. = 102 °C / 0.05 mmHg; R_f = 0.21 (50 % diethyl ether in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.00 (d, ^2J = 6.8 Hz, 1H), 4.88 (d, ^2J = 6.8 Hz, 1H), 4.24 (dtdd, J = 9.3, J = 7.4, $^4J_{H\text{-}F}$ = 3.6, 2.0 Hz, 1H), 3.96 (ddd, ^2J = 10.8, J = 6.4, 3.5 Hz, 1H), 3.78 (ddd, ^2J = 10.8, J = 5.0, 3.1 Hz, 1H), 3.66-3.53 (m, 2H), 3.40 (s, 3H,), 3.20 (d, J = 9.3 Hz, 1H), 1.79-1.52 (m, 2H), 1.41-1.20 (m, 8H), 0.88 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.7 (dd, $^1J_{C\text{-}F}$ = 291.6, 284.7 Hz), 118.2 (dd, $^2J_{C\text{-}F}$ = 36.3. 9.8 Hz), 98.0, 71.4 , 68.4, 67.1, 58.9, 33.9, 31.7, 29.0, 25.4, 22.5, 13.9 ppm; ^{19}F (376 MHz, $CDCl_3$): δ = -100.5 (d, ^2J = 63.7 Hz, 1F), -110.1 (d, ^2J = 63.7 Hz, 1F) ppm; (the ^{19}F-^{1}H splitting was not resolved in the ^{19}F NMR spectrum); $\bar{\nu}$/(neat) = 3421, 2924, 1749, 1232, 1054, 955 cm^{-1}; HRMS (ESI): calcd for $C_{13}H_{24}F_2O_4Na$, 305.1535 $[M+Na]^+$, found: 305.1532; MS (CI): *m/z* (%): 283 (1) $[M+H]^+$, 265 (2) $[M\text{-}OH]^+$, 89 (78) $[C_4H_9O_2]^+$, 59 (100) $[C_3H_7O]^+$; t_R (GC) = 12.41 minutes.

*1,1 Difuoro-2-((2-methoxyethoxy)methoxy) 3-cyclohexyl prop-2-en-3-ol (**3l**)* Prepared as for *trans*-**3a** and *cis*-**3a** from acetal (1.90 mL, 12 mmol), *n*-butyllithium (11.9 mL of a 2.10 M solution in hexanes, 25 mmol), di*iso*propylamine (3.70 mL, 26 mmol) and cyclohexanecarboxaldehyde (1.34 g, 12 mmol) in THF (12 mL). The crude allylic alcohol

(3.12 g) was purified by Kugelrohr distillation to afford **3l** as a pale yellow oil (2.60 g, 77 %). b.p. = 102 °C / 0.06 mmHg; R_f = 0.3 (50 % diethyl ether in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.01 (d, ^2J = 6.8 Hz, 1H), 4.87 (d, ^2J = 6.8 Hz, 1H), 3.96 (ddd, ^2J = 10.8, J = 6.0, 3.1 Hz, 1H), 3.87 (br. d, J = 8.3 Hz, 1H), 3.78 (ddd, ^2J = 10.8, J = 4.8, 3.0 Hz, 1H), 3.65-3.53 (m, 2H), 3.40 (s, 3H), 3.18 (br. s, 1H), 2.10 (br. d, ^2J = 13.7 Hz, 1H), 1.86-1.52 (m, 5H), 1.34-1.10 (m, 3H), 1.08-0.94 (m, 1H), 0.94-0.79 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6 (dd, $^1J_{C\text{-}F}$ = 292.2, 285.2 Hz), 117.0 (dd, $^2J_{C\text{-}F}$ = 37.7. 10.0 Hz), 97.5 (t, $^4J_{C\text{-}F}$ = 3.6 Hz), 71.2, 70.9, 68.0, 58.4, 40.2, 29.0, 28.3, 25.9, 25.3, 25.2 ppm; ^{19}F (376 MHz, $CDCl_3$): δ = -100.6 (d, ^2J = 65.5 Hz, 1F), -110.6 (d, ^2J = 65.5 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3463, 2921, 1749, 1232, 1013, 953 cm^{-1}; HRMS (APCI): calcd for $C_{13}H_{26}F_2O_4N_1$, 298.1824 $[M+NH_4]^+$, found: 298.1819; MS (EI): *m/z* (%): 204 (2) $[M\text{-}C_4H_9F]^+$, 89 (100) $[C_4H_9O_2]^+$, 59 (100) $[C_3H_7O]^+$; t_R (GC) = 12.65 minutes.

*1,1-difluoro-2-((2-methoxyethoxy)methoxy)-3-(tetrahydro-2H-pyran-4-yl)prop-2-en-3-ol (**3m**)*. Prepared as for *trans*-**3a** and *cis*-**3a** from acetal (1.90 mL, 12 mmol), *n*-butyllithium (11.9 mL of a 2.10 M solution in hexanes, 25 mmol), di*iso*propylamine (3.70 mL, 26 mmol) and 4-formyltetrahydropyran (1.37 g, 12 mmol) in THF (12 mL). The crude allylic alcohol (2.71 g) was purified by flash column chromatography (90 g cartridge, 90 % diethyl ether in hexane) to afford **3m** as a pale yellow oil (1.94 g, 57 %). R_f = 0.30 (90 % diethyl ether in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.00 (d, J = 6.6 Hz, 1H), 4.88 (d, J = 6.6 Hz, 1H), 4.09-3.84 (m, 4H), 3.77 (ddd, ^2J = 10.8, J = 4.5, 3.1 Hz, 1H), 3.65-3.52 (m, 2H), 3.45-3.30 (m, 6H), 2.03-1.92 (m, 1H), 1.91-1.75 (m, 1H), 1.52-1.31 (m, 2H),1.23 (qd, J = 11.9, 4.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.7 (dd, $^1J_{C\text{-}F}$ = 292.8, 285.6 Hz), 116.5 (dd, $^2J_{C\text{-}F}$ = 37.2, 11.0 Hz), 97.4 (t, $^4J_{C\text{-}F}$ = 3.8 Hz), 70.9, 70.8 (t, $^3J_{C\text{-}F}$ = 3.0 Hz), 68.0, 67.2, 66.9, 58.5, 37.6, 29.3, 28.2 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -99.7 (d, ^2J =

64.0 Hz, 1F), -109.9 (d, ^2J = 64.0 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3404, 2915, 1749, 1230, 1026, 955 cm^{-1}; HRMS (ESI): calcd for $C_{12}H_{24}F_2O_5N_1$, 300.1617 $[M+NH_4]^+$, found: 300.1620; MS (EI): *m/z* (%): 281 (1) $[M-H]^+$, 89 (92) $[C_4H_9O_2]^+$, 59 (100) $[C_3H_7O]^+$; t_R (GC) = 12.88 minutes.

*1,1-difluoro-2-((2-methoxyethoxy)methoxy)-3-(4-(trifluoromethyl)phenyl)prop-2-en-3-ol (**3o**)*. Prepared as for *trans*-**3a** and *cis*-**3a** from acetal (1.90 mL, 12 mmol), *n*-butyllithium (11.9 mL of a 2.10 M solution in hexanes, 25 mmol), di*iso*propylamine (3.70 mL, 26 mmol) and *p*-trifluoromethylbenzaldehyde (2.09 g, 12 mmol) in THF (12 mL). The crude allylic alcohol (4.99 g) was purified by Kugelrohr distillation followed by flash column chromatography (90 g cartridge, 60 % diethyl ether in petroleum ether) to afford **3o** as a colourless oil (0.87 g, 21 %). b.p. = 113 °C / 0.05 mmHg; R_f = 0.62 (5 % acetone in dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 5.53 (br. d, *J* = 8.7 Hz, 1H), 4.93 (d, ^2J = 6.7 Hz, 1H), 4.87 (d, ^2J = 6.7 Hz, 1H), 3.85 (d, *J* = 8.7 Hz, 1H), 3.76 (ddd, ^2J = 10.8, *J* = 5.9, 3.8 Hz, 1H), 3.64 (ddd, ^2J = 10.8, *J* = 4.9, 3.1 Hz, 1H), 3.58-3.48 (m, 2H), 3.39 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.5 (dd, $^1J_{C\text{-}F}$ = 293.4, 287.4 Hz), 143.9, 129.3 (q, $^2J_{C\text{-}F}$ = 32.3 Hz), 125.8, 124.7 (q, $^3J_{C\text{-}F}$ = 3.5 Hz), 123.6 (q, $^1J_{C\text{-}F}$ = 271.8 Hz), 117.3 (dd, $^2J_{C\text{-}F}$ = 36.0, 11.3 Hz), 97.3 (t, $^4J_{C\text{-}F}$ = 3.9 Hz), 70.7, 68.0, 67.5 (d, $^3J_{C\text{-}F}$ = 3.4 Hz), 58.4 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.5 (s, 3F), -98.5 (dd, ^2J = 60.1, $^4J_{F\text{-}H}$ = 2.0 Hz, 1F), -108.5 (dd, ^2J = 60.1, $^4J_{F\text{-}H}$ = 3.2 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3419, 2930, 1751, 1325, 1112, 1067, 1017 cm^{-1}; HRMS (APCI): calcd for $C_{14}H_{19}F_5O_4N_1$, 360.1229 $[M+NH_4]^+$, found: 360.1231; MS (EI): *m/z* (%): 323 (1) $[M-F]^+$, 175 (9) $[C_8H_6F_3O]^+$, 89 (63) $[C_4H_9O_2]^+$, 59 (100) $[C_3H_7O]^+$; t_R (GC) = 12.49 minutes.

General Procedure B: Difluorinated Diol Preparation. *(1R*,3R*,4aS*,8aS*)-2,2-difluoro-3-methyloctahydronaphthalene-1,8a(1H)-diol (1, 3-trans, 1, 8a-trans-**4a**) and*

(1R,3S*,4aS*,8aS*)-2,2-difluoro-3-methyloctahydronaphthalene-1,8a(1H)-diol (1, 3-cis, 1, 8a-trans-**4a**)*.1,3-*Bis*(2,6-di*iso*propylphenyl-imidazol-2-ylidene)gold(I) chloride (5 mol %, 0.031 g) was taken up in dichloromethane (1 mL) and added *via* syringe to dichloromethane (3.4 mL). The solution was stirred at room temperature then a solution of silver hexafluoroantimonate(V) (5 mol %, 0.017 g) in methanol (0.6 mL) was added as a stream *via* syringe. An off-white precipitate formed after the addition was complete. The flask was fitted with an air condenser (open to the atmosphere), and the suspension was heated to 40 °C. A solution of allyl alcohol *trans*-**3a** and *cis*-**3a** (0.306 g, 1 mmol) in dichloromethane (1 mL) was added in a stream *via* syringe. After stirring for 5 hours at 40 °C the reaction was allowed to cool to room temperature. Solid tetrabutylammonium borohydride (0.258 g, 1 mmol) was added to the flask in small portions. A slight effervescence was observed as the reducing agent was added and the reaction mixture darkened from colourless to dark brown. The reaction mixture was then allowed to stir at room temperature for 18 hours, then was quenched with hydrogen peroxide (10 mL of a 3wt % aqueous solution), followed by sodium hydroxide (5 mL of a 10wt% aqueous solution). The mixture was transferred to a separating funnel and the organic layer was removed. The aqueous layer was extracted with dichloromethane (4 x 40 mL). The combined organic extracts were then washed with sodium sulfite (10 mL of a saturated aqueous solution). The organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product as aviscous pale yellow oil (0.280 g). The crude material was purified by flash column chromatography (40 g silica, 2 % acetone in dichloromethane) to afford an inseparable mixture of *1, 3-trans, 1, 8a-trans*-**4a** and *1, 3-cis, 1, 8a-trans*-**4a** as a colourless solid (0.154 g, 70 %, 2.6:1). R_f = 0.47 (5 % acetone in dichloromethane); The following signals were attributed to both the minor *1, 3-cis, 1, 8a-trans*-diastereoisomer **4a** and major *1, 3-trans, 1, 8a-trans* -diastereoisomer **4a** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.60-3.47 (m, 1H), 2.42-2.17 (m, 1H),

1.97-1.27 (envelope, 17H) ppm; The following signals were attributed to the major *1, 3-trans, 1, 8a-trans*-diastereoisomer **4a** (assigned on the basis of δ and intensity); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14 (t, *J* = 2.8 Hz, 1H), 1.06 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 124.0 (t, $^{1}J_{C\text{-}F}$ = 248.2 Hz), 74.2 (dd, $^{2}J_{C\text{-}F}$ = 27.7, 21.4 Hz), 72.7 (d, $^{3}J_{C\text{-}F}$ = 5.2 Hz), 36.6, 33.7, 32.8 (t, $^{2}J_{C\text{-}F}$ = 21.4 Hz), 32.6 (d, $^{3}J_{C\text{-}F}$ = 8.5 Hz), 26.6, 25.1, 19.8, 11.2 (d, $^{3}J_{C\text{-}F}$ = 5.6 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -105.9 (dq, ^{2}J = 256.5, $^{3}J_{F\text{-}H}$ = $^{4}J_{F\text{-}H}$ = 4.8 Hz, 1F), -116.6 (ddt, ^{2}J = 256.5, $^{3}J_{F\text{-}H}$ = 30.3, $^{3}J_{F\text{-}H}$ = $^{4}J_{F\text{-}H}$ = 7.6 Hz, 1F) ppm; The following signals were attributed to the minor *1, 3-cis, 1, 8a-trans*--diastereoisomer **4a** (assigned on the basis of δ and intensity); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.11 (t, *J* = 2.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 123.4 (dd, $^{1}J_{C\text{-}F}$ = 253.8, 242.5 Hz), 75.3 (dd, $^{2}J_{C\text{-}F}$ = 28.9, 21.7 Hz), 72.3 (d, $^{3}J_{C\text{-}F}$ = 5.8 Hz), 35.1 (dd, $^{2}J_{C\text{-}F}$ = 23.4, 21.0 Hz), 31.1, 30.8 (d, $^{3}J_{C\text{-}F}$ = 7.3 Hz), 26.8, 25.3, 19.9, 14.2 (dd, $^{3}J_{C\text{-}F}$ = 9.4, 3.7 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -93.6 (ddt, ^{2}J = 261.3, $^{3}J_{F\text{-}H}$ = 17.6, $^{3}J_{F\text{-}H}$ = $^{4}J_{F\text{-}H}$ = 8.0 Hz), -104.5 (d, ^{2}J = 261.3 Hz) ppm; $\bar{\nu}$/(neat) = 3608, 3450, 2919, 1446, 1069, 985 cm^{-1}; HRMS (ASAP): calcd for $C_{11}H_{17}F_2O_2$, 219.1197 $[M\text{-}H]^+$, found: 219.1194; MS (EI): *m/z* (%): 220 (3) $[M]^+$, 182 (13) $[M\text{-}2F]^+$; t_R (GC) = 11.27 minutes;* elemental analysis calcd (%) for $C_{11}H_{18}F_2O_2$: C, 59.98; H, 8.24; found**:** C, 59.75; H, 8.17. This analysis was obtained for the amorphous solid obtained following chromatography so no melting point was recorded.* the individual diastereoisomers appeared as one peak by GC. Diastereomerically pure *1, 3-trans, 1, 8a-trans*-**4a** could be obtained by performing three vapour diffusion recrystallizations (chloroform/pentane) of the mixed solid diol (0.024g, 11%). m.p. = 84-86 °C (recrystallized from chloroform/pentane vapour diffusion as a colourless plate); R_f = 0.47 (5 % acetone in dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.54 (td, $J_{H\text{-}F}$ = 6.0, *J* = 3.2 Hz, 1H), 2.38-2.16 (m, 1H), 2.14 (td, *J* = $^{4}J_{H\text{-}F}$ = 3.0, $^{4}J_{H\text{-}F}$ = 1.0 Hz, 1H), 1.85 (tdd, ^{2}J = *J* = 13.3, *J* = 4.9, ^{4}J = 1.2 Hz, 1H), 1.80-1.19 (envelope, 11H), 1.08 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR

(100 MHz, $CDCl_3$): δ = 124.0 (t, $^1J_{C\text{-}F}$ = 248.2 Hz), 74.2 (dd, $^2J_{C\text{-}F}$ = 27.7, 21.4 Hz), 72.7 (d, $^3J_{C\text{-}F}$ = 5.2 Hz), 36.6, 33.7, 32.8 (t, $^2J_{C\text{-}F}$ = 21.4 Hz), 32.6 (d, $^3J_{C\text{-}F}$ = 8.5 Hz), 26.6, 25.1, 19.8, 11.2 (d, $^3J_{C\text{-}F}$ = 5.6 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -105.9 (dq, ^2J = 256.5, $^3J_{F\text{-}H}$ = $^4J_{F\text{-}H}$ = 4.8 Hz), -116.6 (ddt, ^2J = 256.5, $^3J_{F\text{-}H}$ = 30.3, $^3J_{F\text{-}H}$ = $^4J_{F\text{-}H}$ = 7.6 Hz) ppm; $\bar{\nu}$/(neat) = 3617, 3450, 2922, 1446, 1068, 985, 957 cm^{-1}; MS (EI): *m/z* (%): 220 (2) $[M]^+$, 182 (19) $[M\text{-}2F]^+$; t_R (GC) = 11.27 minutes; elemental analysis calcd (%) for $C_{11}H_{18}F_2O_2$: C, 59.98; H, 8.24; found**:** C, 60.12; H, 8.48.

(2R,4R*,4aS*,9aS*)-3,3-Difluoro-2-methyldecahydro-4aH-benzo[7]annulene-4,4a-diol (1, 3-trans, 1, 9a-trans-**4b**) and (2S*,4R*,4aS*,9aS*)-3,3-difluoro-2-methyldecahydro-4aH-benzo[7]annulene-4,4a-diol (1, 3-cis, 1, 9a-trans-**4b**)*. Prepared according to general procedure B from *trans*-**3b** and *cis*-**3b** (0.320 g, 1.00 mmol) with 1,3-*bis*(2,6-di*iso*propylphenyl-imidazol-2-ylidene)gold(I) chloride (5 mol %, 0.031 g) and silver hexafluoroantimonate(V) (5 mol %, 0.017 g) in dichloromethane (5.4 mL) and methanol (0.6 mL). After stirring for 5 hours at 40 °C the reaction was allowed to cool to room temperature and reduced with tetrabutylammonium borohydride (0.258 g, 1 mmol). The usual work up afforded a viscous pale yellow oil (0.323 g) which was purified by flash column chromatography (40 g silica, 1 % acetone in dichloromethane) to afford an inseparable mixture of *1, 3-trans, 1, 9a-trans*-**4b** and *1, 3-cis, 1, 9a-trans*-**4b** as a colourless solid (0.162 g, 69 %, 4.9:1). R_f = 0.34 (1 % acetone in dichloromethane); The following signals were attributed to both the minor *1, 3-cis, 1, 9a-trans*-diastereoisomer **4b** and major *1, 3-trans, 1, 9a-trans*-diastereoisomer **4b** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.52 (td, $J_{H\text{-}F}$ = 5.9, J = 3.2 Hz, 1H), 1.99-1.17 (envelope, 15H) ppm; The following signals were attributed to the major *1, 3-trans, 1, 9a-trans*-diastereoisomer **4b** (assigned on the basis of δ and intensity); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.35-2.14 (m, including 2.29 (t, J = $^4J_{H\text{-}F}$ = 3.2 Hz, 1H), 1H), 2.09-1.99 (m, 1H), 1.04 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, MeOD): δ = 123.1 (t, $^1J_{C\text{-}F}$ = 248.3 Hz), 75.5 (dd, $^2J_{C\text{-}F}$ = 27.6,

20.5 Hz), 74.6 (d, $^{3}J_{C\text{-}F}$ = 5.5 Hz), 40.2, 39.2, 34.3 (d, $^{3}J_{C\text{-}F}$ = 8.5 Hz), 32.6 (t, $^{2}J_{C\text{-}F}$ = 22.0 Hz), 28.0, 27.0, 26.1, 19.8, 10.2 (d, $^{3}J_{C\text{-}F}$ = 5.7 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -107.6 (app. ds, ^{2}J = 256.3, $^{3}J_{F\text{-}H}$ = $^{4}J_{F\text{-}H}$ = 3.2 Hz, 1F), -117.1 (dddd, ^{2}J = 256.3, $^{3}J_{F\text{-}H}$ = 30.2, $^{3}J_{F\text{-}H}$ = 8.9, $^{4}J_{F\text{-}H}$ = 6.0 Hz, 1F) ppm; The following signals were attributed to the minor *1, 3-cis, 1, 9a-trans*-diastereoisomer **4b** (assigned on the basis of δ and intensity); ^{13}C NMR (100 MHz, MeOD): δ = 122.7 (dd, $^{1}J_{C\text{-}F}$ = 251.0, 243.2 Hz), 76.6 (dd, $^{2}J_{C\text{-}F}$ = 28.7, 20.5 Hz), 74.3 (d, $^{3}J_{C\text{-}F}$ = 5.4 Hz), 39.0, 35.0, 34.9 (dd, $^{2}J_{C\text{-}F}$ = 23.8, 21.1 Hz), 32.6 (d, $^{3}J_{C\text{-}F}$ = 6.4 Hz), 28.2, 27.1, 26.3, 13.4 (dd, $^{3}J_{C\text{-}F}$ = 9.7, 4.0 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -93.7 (ddt, ^{2}J = 261.3, $^{3}J_{F\text{-}H}$ = 18.3, $^{3}J_{F\text{-}H}$ = $^{4}J_{F\text{-}H}$ = 8.1 Hz), -106.5 (d, ^{2}J = 261.3 Hz) ppm; $\bar{\nu}$/(neat) = 3601, 3333, 2908, 1463, 1084, 979 cm^{-1}; HRMS (APCI): calcd for $C_{12}H_{20}F_2O_2$, 234.1431 $[M]^+$, found: 234.1432; MS (EI): *m/z* (%): 234 (1) $[M]^+$, 196 (9) $[M\text{-}2F]^+$; t_R (GC) = 12.80 minutes.* elemental analysis calcd (%) for $C_{12}H_{20}F_2O_2$: C, 61.52; H, 8.60; found**:** C, 61.40; H, 8.38. This analysis was obtained for the amorphous solid obtained following chromatography so no melting point was recorded.* the individual diastereoisomers appeared as one peak by GC. Diastereomerically pure *1, 3-trans, 1, 9a-trans*-**4b** could be obtained by performing three vapour diffusion recrystallizations (chloroform/pentane) of the mixed solid diol (0.018g, 7%). m.p. = 96-98 °C (recrystallized from chloroform/pentane vapour diffusion as a colourless plate); R_f = 0.34 (1 % acetone in dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.54 (td, $J_{H\text{-}F}$ = 5.9, J = 3.2 Hz, 1H), 2.36-2.15 (m, 2H), 2.12-1.99 (m, 1H), 1.90-1.23 (envelope, 13H), 1.06 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 124.0 (t, $^{1}J_{C\text{-}F}$ = 247.8 Hz), 76.1 (dd, $^{2}J_{C\text{-}F}$ = 27.4, 20.8 Hz), 74.8 (d, $^{3}J_{C\text{-}F}$ = 5.1 Hz), 40.2, 39.2, 34.3 (d, $^{3}J_{C\text{-}F}$ = 8.6 Hz), 32.5 (t, $^{2}J_{C\text{-}F}$ = 21.7 Hz), 28.1, 27.2, 26.3, 20.0, 11.0 (d, $^{3}J_{C\text{-}F}$ = 5.2 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = = -107.6 (app. ds, ^{2}J = 256.3, $^{3}J_{F\text{-}H}$ = $^{4}J_{F\text{-}H}$ = 3.2 Hz, 1F), -117.1 (dddd, ^{2}J = 256.3, $^{3}J_{F\text{-}H}$ = 30.2, $^{3}J_{F\text{-}H}$ = 8.9, $^{4}J_{F\text{-}H}$ = 6.0 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3601, 3333, 2908, 1463, 1084, 979 cm^{-1}; MS (EI): *m/z* (%): 234 (1) $[M]^+$, 196 (9) $[M\text{-}2F]^+$; t_R

(GC) = 12.80 minutes. elemental analysis calcd (%) for $C_{12}H_{20}F_2O_2$: C, 61.52; H, 8.60; found**:** C, 61.37; H, 8.50.

(4aS,5R*,7R*,8aR*)-6,6-Difluoro-7-methyloctahydro-4aH-isochromene-4a,5-diol (*4a, 5-*trans*, 5, 7-*trans*-**4c**), (4aS*,5R*,7S*,8aR*)-6,6-difluoro-7-methyloctahydro-4aH-isochromene-4a,5-diol (*4a, 5-*trans*, 5, 7-*cis*-**4c**) and (4aS*,5S*,7R*,8aR*)-6,6-difluoro-7-methyloctahydro-4aH-isochromene-4a,5-diol (*4a, 5-*cis*, 5, 7-*cis*-**4c**)*. Prepared according to general procedure B from *trans*-**3c** and *cis*-**3c** (0.308 g, 1.00 mmol) with 1,3-*bis*(2,6-di*iso*propylphenyl-imidazol-2-ylidene)gold(I) chloride (5 mol %, 0.031 g) and silver hexafluoroantimonate(V) (5 mol %, 0.017 g) in dichloromethane (5.4 mL) and methanol (0.6 mL). After stirring for 6.5 hours at 40 °C the reaction was allowed to cool to room temperature and reduced with tetrabutylammonium borohydride (0.258 g, 1 mmol). The usual work up afforded a viscous pale yellow oil (0.300 g) which was purified by flash column chromatography (40 g silica, 10 % acetone in dichloromethane) to afford an inseparable mixture of 4a, 5-*trans*, 5, 7-*trans*-**4c**, 4a, 5-*trans*, 5, 7-*cis*-**4c** and 4a, 5-*cis*, 5, 7-*cis*-**4c** as a colourless solid (0.107 g, 48 %, 6.7:1.4:1). R_f = 0.39 (20 % acetone in dichloromethane); The following signals were attributed to the minor 4a, 5-*trans*, 5, 7-*cis* -**4c** and 4a, 5-*cis*, 5, 7-*cis* -**4c** diastereoisomers and the major 4a, 5-*trans*, 5, 7-*trans*- diastereoisomer **4c** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.93-3.78 (m, 3H), 3.65-3.46 (m, 4H), 2.47-1.47 (envelope, 6H), 1.43-1.15 (envelope, 4H) ppm; The following signals were attributed to the major 4a, 5-*trans*, 5, 7-*trans* diastereoisomer **4c** (assigned on the basis of δ and intensity); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.70 (t, $J = {}^4J_{H\text{-}F}$ = 3.0 Hz, 1H), 1.09 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 123.7 (dd, $^1J_{C\text{-}F}$ = 250.5, 246.7 Hz), 73.2 (dd, $^2J_{C\text{-}F}$ = 27.7, 21.6 Hz), 70.6 (d, $^3J_{C\text{-}F}$ = 5.7 Hz), 66.1, 62.1, 36.5, 33.6, 32.7 (t, $^2J_{C\text{-}F}$ = 22.1 Hz), 27.1 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 11.2 (dd, $^3J_{C\text{-}F}$ = 6.2, 2.8 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -105.8 (dq, ^2J = 258.4, $^3J_{F\text{-}H} = {}^4J_{F\text{-}H}$ = 4.2 Hz, 1F), -117.1 (dddd, ^2J = 258.4, $^3J_{F\text{-}H}$ = 30.5, $^3J_{F\text{-}H}$ = 10.7, $^4J_{F\text{-}H}$ = 5.9 Hz,

1F) ppm; The following signals were attributed to the 4a, 5-*trans*, 5, 7-*cis* -diastereoisomer **4c** (assigned on the basis of δ and intensity); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.65 (t, $J = {}^{4}J_{H\text{-}F}$ = 2.9 Hz, 1H), 1.12 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 123.1 (dd, $^{1}J_{C\text{-}F}$ = 254.8, 241.6 Hz), 74.3 (dd, $^{2}J_{C\text{-}F}$ = 29.0, 21.9 Hz), 70.4 (d, $^{3}J_{C\text{-}F}$ = 7.7 Hz), 66.5, 62.2, 41.1, 34.8 (t, $^{2}J_{C\text{-}F}$ = 22.5 Hz), 31.3, 27.0 (d, $^{3}J_{C\text{-}F}$ = 8.3 Hz), 14.1 (dd, $^{3}J_{C\text{-}F}$ = 9.9, 4.0 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -93.7 (dddd, ^{2}J = 263.9, $^{3}J_{F\text{-}H}$ = 18.0, 10.4, $^{4}J_{F\text{-}H}$ = 6.7 Hz, 1F), -104.3 (d, ^{2}J = 263.9 Hz, 1F) ppm; The following signals were attributed to the 4a, 5-*cis*, 5, 7-*cis*-diastereoisomer **4c** (assigned on the basis of δ and intensity); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.84 (d, J = 6.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 75.0 (t, $^{2}J_{C\text{-}F}$ = 19.3 Hz), 70.2 (d, $^{3}J_{C\text{-}F}$ = 5.4 Hz), 65.6, 62.7, 36.8 (dd, $^{2}J_{C\text{-}F}$ = 23.3, 21.2 Hz), 34.9, 29.2, 25.3 (d, $^{3}J_{C\text{-}F}$ = 7.0 Hz), 11.3 (dd, $^{3}J_{C\text{-}F}$ = 6.2, 2.9 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = (-106.7) – (-107.6) (m, including -107.1 (app. d, ^{2}J = 243.7 Hz, 1F)), -104.4 (dddd, ^{2}J = 243.7, $^{3}J_{F\text{-}H}$ = 28.2, 20.1, $^{4}J_{F\text{-}H}$ = 4.6 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3331, 2878, 2908, 1472, 1091, 966 cm^{-1}; HRMS (APCI): calcd for $C_{10}H_{17}F_2O_3$, 223.1146 $[M+H]^+$, found: 223.1142; MS (EI): *m/z* (%): 222 (1) $[M]^+$ (major 4a, 5-*trans*, 5, 7-*trans* diastereoisomer, minor 4a, 5-*trans*, 5, 7-*cis* diastereoisomer and minor 4a, 5-*cis*, 5, 7-*cis* diastereoisomer); t_R (GC) = 12.27 minutes (major 4a, 5-*trans*, 5, 7-*trans* diastereoisomer), 12.34 minutes (minor 4a, 5-*trans*, 5, 7-*cis* diastereoisomer), 12.69 (minor 4a, 5-*cis*, 5, 7-*cis* diastereoisomer); elemental analysis calcd (%) for $C_{10}H_{16}F_2O_3$: C, 54.05; H, 7.26; found**:** C, 54.05; H, 6.93. This analysis was obtained for the amorphous solid obtained following chromatography so no melting point was recorded.

tert-Butyl (4aS,5R*,7R*,8aR*)-6,6-difluoro-4a,5-dihydroxy-7-methyloctahydroisoquinoline-2(1H)-carboxylate (*4a, 5-*trans*, 5, 7-*trans*-***4d**), tert-butyl (4aS*,5R*,7S*,8aR*)-6,6-difluoro-4a,5-dihydroxy-7-methyloctahydroisoquinoline-2(1H)-carboxylate (*4a, 5-*trans*, 5, 7-*cis*-***4d**) and tert-butyl (4aS*,5S*,7R*,8aR*)-6,6-difluoro-4a,5-*

*dihydroxy-7-methyloctahydroisoquinoline-2(1H)-carboxylate (*4a, 5-*cis*, 5, 7-*cis*-***4d***). Prepared according to general procedure B from *trans*-**3d** and *cis*-**3d** (0.407 g, 1.00 mmol) with 1,3-*bis*(2,6-di*iso*propylphenyl-imidazol-2-ylidene)gold(I) chloride (5 mol %, 0.031 g) and silver hexafluoroantimonate(V) (5 mol %, 0.017 g) in dichloromethane (5.4 mL) and methanol (0.6 mL). After stirring for 240 hours at 40 °C the reaction was allowed to cool to room temperature and reduced with tetrabutylammonium borohydride (0.258 g, 1 mmol). The usual work up afforded a viscous pale yellow oil (0.434 g) which was purified by flash column chromatography (40 g silica, 5-8 % acetone in dichloromethane) to afford an inseparable mixture of 4a, 5-*trans*, 5, 7-*trans*-**4d**, 4a, 5-*trans*, 5, 7-*cis*-**4d** and 4a, 5-*cis*, 5, 7-*cis*-**4d** as a colourless solid (0.160 g, 50 %, 3.4:0.9:1). R_f = 0.31 (10 % acetone in dichloromethane); The following signals were attributed to the minor 4a, 5-*trans*, 5, 7-*cis*-**4d** and 4a, 5-*cis*, 5, 7-*cis*-**4d** diastereoisomers and the major 4a, 5-*trans*, 5, 7-*trans*-diastereoisomer **4d** ^{1}H NMR (600 MHz, pyridine-d_5, 373 K): δ = 4.35-4.21 (m, 1H), 4.20-4.05 (m, 1H), 3.69-3.27 (m, 2H), 3.28-3.06 (m, 1H), 2.63-2.35 (m, 2H), 2.33-2.14 (m, 1H), 2.14-1.77 (m, 1H), 1.77-1.51 (m, including 1.60 (s, 9H), 15H), 1.39-1.22 (m, 2H) ppm; The following signals were attributed to the major 4a, 5-*trans*, 5, 7-*trans*-diastereoisomer **4d** (assigned on the basis of δ and intensity); ^{1}H NMR (600 MHz, pyridine-d_5, 373 K): δ = 6.97 (br. s, 1H), 4.59 (br. s, 1H), 3.95 (t, $J = {}^4J_{H\text{-}F}$ = 6.2 Hz, 1H), 1.17 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.3, 123.8 (dd, $^1J_{C\text{-}F}$ = 251.5, 246.5 Hz), 79.1, 73.3 (dd, $^2J_{C\text{-}F}$ = 27.8, 21.9 Hz), 71.2 (d, $^3J_{C\text{-}F}$ = 5.7 Hz), 11.1 (d, $^3J_{C\text{-}F}$ = 5.1Hz) ppm; The ^{13}C NMR spectral region ranging from 46-26 ppm was poorly resolved at 298 K. The ^{13}C NMR spectrum was recorded in pyridine-d_5 at 373 K to resolve this region; ^{13}C NMR (150 MHz, pyridine-d_5, 373 K): δ = 44.2, 39.3, 37.4, 34.8, 33.6 (t, $^2J_{C\text{-}F}$ = 22.5 Hz), 30.0 (d, $^3J_{C\text{-}F}$ = 8.4 Hz), 28.4 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -106.2 (dq, ^2J = 258.2, $^3J_{F\text{-}H} = {}^4J_{F\text{-}H}$ = 4.7 Hz, 1F), -117.1 (br. ddt, ^2J = 258.2, $^3J_{F\text{-}H}$ = 30.0, $^3J_{F\text{-}H} = {}^4J_{F\text{-}H}$ = 6.5 Hz, 1F) ppm (the ^{19}F

NMR spectrum was well resolved at 273 K and did not require heating. ^{1}H and ^{13}C NMR resolved slightly better when heated to 373 K); The following signals were attributed to the 4a, 5-*trans*, 5, 7-*cis*-diastereoisomer **4d** (assigned on the basis of δ and intensity); ^{1}H NMR (600 MHz, pyridine-d_5, 373 K): δ = 1.41 (d, J = 7.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 79.2, 74.4 (dd, $^{2}J_{C\text{-}F}$ = 28.9, 21.7 Hz), 71.1 (d, $^{3}J_{C\text{-}F}$ = 7.9 Hz), 14.2 (dd, $^{3}J_{C\text{-}F}$ = 9.9, 3.4 Hz) ppm; The ^{13}C NMR spectral region ranging from 46-26 ppm was poorly resolved at 298 K. The ^{13}C NMR spectrum was recorded in pyridine-d_5 at 373 K to resolve this region; ^{13}C NMR (150 MHz, pyridine-d_5, 373 K): δ = 44.7, 39.7, 37.7 (t, $^{2}J_{C\text{-}F}$ = 22.1 Hz), 35.5, 29.8 (d, $^{3}J_{C\text{-}F}$ = 7.8 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -93.1 (dddd, ^{2}J = 263.9, $^{3}J_{F\text{-}H}$ = 18.0, 10.4, $^{4}J_{F\text{-}H}$ = 6.8 Hz, 1F), -104.7 (d, ^{2}J = 263.9 Hz, 1F) ppm; The following signals were attributed to the 4a, 5-*cis*, 5, 7-*cis*-diastereoisomer **4d** (assigned on the basis of δ and intensity); ^{1}H NMR (600 MHz, pyridine-d_5, 373 K): δ = 4.63 (br. s, 1H), 3.99 (t, J = $^{4}J_{H\text{-}F}$ = 6.3 Hz, 1H), 3.76 (dd, $J_{H\text{-}F}$ = 20.2, J = 6.3 Hz, 1H), 1.16 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 79.1, 74.9 (t, $^{2}J_{C\text{-}F}$ = 20.4 Hz), 70.8 (d, $^{3}J_{C\text{-}F}$ = 5.8 Hz), 11.3 (dd, $^{3}J_{C\text{-}F}$ = 5.6, 2.9 Hz) ppm; The ^{13}C NMR spectral region ranging from 46-26 ppm was poorly resolved at 298 K. The ^{13}C NMR spectrum was recorded in pyridine-d_5 at 373 K to resolve this region; ^{13}C NMR (150 MHz, pyridine-d_5, 373 K): δ = 43.9, 41.7, 39.3, 36.1 (t, $^{2}J_{C\text{-}F}$ = 23.2 Hz), 32.3, 28.5 (d, $^{3}J_{C\text{-}F}$ = 7.1 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -107.6 (d, ^{2}J = 243.7 Hz, 1F), -116.1 (ddd, ^{2}J = 243.7, $^{3}J_{F\text{-}H}$ = 27.4, 20.2 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3274, 2924, 1656, 1158, 870 cm^{-1}; HRMS (APCI): calcd for $C_{15}H_{26}F_2O_4N_1$, 322.1830 $[M+H]^+$, found: 322.1831; MS (EI): *m/z* (%): 321 (3) $[M]^+$, 247 (23) $[M\text{-}C_4H_{10}O]^+$ (major 4a, 5-*trans*, 5, 7-*trans* diastereoisomer), 321 (1) $[M]^+$, 247 (24) $[M\text{-}C_4H_{10}O]^+$ (minor 4a, 5-*trans*, 5, 7-*cis* diastereoisomer), 321 (2) $[M]^+$, 247 (22) $[M\text{-}C_4H_{10}O]$ (minor 4a, 5-*cis*, 5, 7-*cis* diastereoisomer); t_R (GC) = 15.06 minutes (major 4a, 5-*trans*, 5, 7-*trans* diastereoisomer), 15.15 minutes (minor 4a, 5-*trans*, 5, 7-*cis* diastereoisomer), 14.99 (minor 4a, 5-*cis*, 5, 7-*cis*

diastereoisomer); elemental analysis calcd (%) for $C_{15}H_{25}F_2NO_4$: C, 56.06; H, 7.84; N, 4.36; found**:** C, 56.37; H, 7.86; N, 4.34. This analysis was obtained for the amorphous solid obtained following chromatography so no melting point was recorded.

(1R,2S*,4S*)-3,3-Difluoro-1,4-dimethylcyclohexane-1,2-diol (*1, 2-*trans*, 2, 4-*trans* - **4ea**), (1S*,2R*,4S*)-3,3-difluoro-1,4-dimethylcyclohexane-1,2-diol (*1, 2-*trans*, 2, 4-*cis*-**4eb**) and (1R*,2R*,4S*)-3,3-difluoro-1,4-dimethylcyclohexane-1,2-diol (*1, 2-*cis*, 2, 4-*cis*-**4ec**)*. Prepared according to general procedure B from **3e** (0.327 g, 1.23 mmol) with 1,3-*bis*(2,6-di*iso*propylphenyl-imidazol-2-ylidene)gold(I) chloride (5 mol %, 0.038 g) and silver hexafluoroantimonate(V) (5 mol %, 0.021 g) in dichloromethane (6.6 mL) and methanol (0.7 mL). After stirring for 18 hours at 40 °C the reaction was allowed to cool to room temperature and reduced with tetrabutylammonium borohydride (0.317 g, 1.23 mmol). The usual work up afforded a viscous pale yellow oil (0.320 g) which was purified by flash column chromatography (40 g silica, 30 % ethyl acetate in hexane) to afford a mixture of 1, 2-*cis*, 2, 4-*cis*-**4ec** and 1, 2-*trans*, 2, 4-*trans*-**4ea** as a pale yellow oil (33.7 mg, 15 %, 1.2:1), 1, 2-*trans*, 2, 4-*trans*-**4ea** as a pale yellow oil (55.5 mg, 25 %) and 1, 2-*trans*, 2, 4-*cis*-**4eb** as a colourless solid (35.6 mg, 16 %). R_f 1, 2-*trans*, 2, 4-*trans*-**4ea** = 0.31 (10 % acetone in dichloromethane); R_f 1, 2-*cis*, 2, 4-*cis*-**4ec** = 0.25 (10 % acetone in dichloromethane); The following signals were attributed to both the major 1, 2-*cis*, 2, 4-*cis*-diastereoisomer **4ec** and minor 1, 2-*trans*, 2, 4-*trans*-diastereoisomer **4ea** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.35-1.97 (m, 3H), 1.95-1.68 (m, 3H), 1.68-1.42 (m, 5H) ppm; The following signals were attributed to the major 1, 2-*cis*, 2, 4-*cis*-diastereoisomer **4ec** (assigned on the basis of δ and intensity); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.48 (dd, $J_{H\text{-}F}$ = 20.3, 6.0 Hz, 1H), 1.34 (s, 3H), 1.11 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 121.9 (t, $^1J_{C\text{-}F}$ = 246.8 Hz), 74.3 (t, $^2J_{C\text{-}F}$ = 20.3 Hz), 71.9 (d, $^3J_{C\text{-}F}$ = 6.9 Hz), 36.7 (dd, $^2J_{C\text{-}F}$ = 23.3, 20.5 Hz), 35.3, 25.9, 24.8 (d, $^4J_{C\text{-}F}$ = 7.8 Hz), 11.0 (d, $^3J_{C\text{-}F}$ = 4.3 Hz) ppm; ^{19}F NMR (376 MHz, DMSO-d_6, 373 K): δ = -104.6 (d,

^{2}J = 238.7 Hz, 1F), -127.9 (dt, ^{2}J = 238.7, $^{3}J_{F\text{-}H}$ = 20.3 Hz, 1F) ppm (the ^{1}H and ^{13}C NMR gave clear well resolved spectra at RT and did not require heating. ^{19}F NMR resolved better when heated to 373 K); The following signals were attributed to the minor 1, 2-*trans*, 2, 4-*trans*-diastereoisomer **4ea** (assigned on the basis of δ and intensity); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.63 (dd, $J_{H\text{-}F}$ = 8.1, 6.7 Hz, 1H), 1.33 (s, 3H), 1.08 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 123.4 (t, $^{1}J_{C\text{-}F}$ = 248.1 Hz), 73.4 (dd, $^{2}J_{C\text{-}F}$ = 26.8, 21.6 Hz), 72.3 (d, $^{3}J_{C\text{-}F}$ = 4.3 Hz), 31.9 (t, $^{2}J_{C\text{-}F}$ = 21.4 Hz), 31.5, 24.7 (d, $^{3}J_{C\text{-}F}$ = 7.4 Hz), 24.7 (d, $^{4}J_{C\text{-}F}$ = 7.4 Hz), 10.9 (d, $^{3}J_{C\text{-}F}$ = 4.5 Hz) ppm; ^{19}F NMR (376 MHz, DMSO-d_6, 373 K): δ = -104.2 (d, ^{2}J = 243.2 Hz, 1F), -114.0 (dd, ^{2}J = 243.2, $^{3}J_{F\text{-}H}$ = 25.8 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3392, 2941, 1461, 1066, 994 cm^{-1}; HRMS (ESI): calcd for $C_8H_{18}F_2O_2N_1$, 198.1300 $[M+NH_4]^+$, found: 198.1300; MS (EI): *m/z* (%): 142 (8) $[M\text{-}2F]^+$ (major 1, 2-*cis*, 2, 4-*cis* diastereoisomer), 142 (7) $[M\text{-}2F]^+$ (minor 1, 2-*trans*, 2, 4-*trans* diastereoisomer); t_R (GC) = 8.77 minutes (major 1, 2-*cis*, 2, 4-*cis* diastereoisomer), 8.54 minutes (minor 1, 2-*trans*, 2, 4-*trans* diastereoisomer). Diastereomerically pure 1, 2-*trans*, 2, 4-*trans*-**4ea**: R_f = 0.31 (10 % acetone in dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.62 (dd, $J_{H\text{-}F}$ = 8.1, 6.7 Hz, 1H), 2.81 (br. s, 1H), 2.40-1.97 (m, 2H), 1.81-1.69 (m, 1H), 1.67-1.45 (m, 3H), 1.33 (s, 3H), 1.07 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 123.9 (t, $^{1}J_{C\text{-}F}$ = 247.0 Hz), 73.9 (dd, $^{2}J_{C\text{-}F}$ = 26.9, 21.7 Hz), 72.8 (d, $^{3}J_{C\text{-}F}$ = 4.2 Hz), 32.4 (t, $^{2}J_{C\text{-}F}$ = 21.8 Hz), 32.0, 25.2 (d, $^{3}J_{C\text{-}F}$ = 7.3 Hz), 25.2 (d, $^{4}J_{C\text{-}F}$ = 7.3 Hz), 11.5 (t, $^{3}J_{C\text{-}F}$ = 4.1 Hz) ppm; ^{19}F NMR (376 MHz, DMSO-d_6, 373 K): δ = -104.2 (d, ^{2}J = 243.2 Hz, 1F), -114.0 (dd, ^{2}J = 243.2, $^{3}J_{F\text{-}H}$ = 25.8 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3392, 2941, 1461, 1066, 994 cm^{-1}; MS (EI): *m/z* (%): 142 (7) $[M\text{-}2F]^+$; t_R (GC) = 8.54 minutes; Diastereomerically pure 1, 2-*trans*, 2, 4-*cis*-**4eb**: m.p. = 58-60 °C (recrystallized from chloroform/pentane vapour diffusion as a colourless plate); R_f = 0.33 (20 % acetone in dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.71 (dd, $J_{H\text{-}F}$ = 22.5, 4.6 Hz, 1H), 2.81 (br. s, 1H), 2.64 (s, 1H), 1.99-1.76 (m, 2H), 1.74-1.54 (m, 2H), 1.34 (td, $^{2}J = J$

= 13.7, J = 4.9 Hz, 1H) 1.27 (d, $^{5}J_{H\text{-}F}$ = 2.3 Hz, 3H), 1.09 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 121.9 (dd, $^{1}J_{C\text{-}F}$ = 249.0, 245.2 Hz), 77.9 (t, $^{2}J_{C\text{-}F}$ = 20.5 Hz), 73.4 (d, $^{3}J_{C\text{-}F}$ = 7.8 Hz), 37.1 (t, $^{2}J_{C\text{-}F}$ = 21.8 Hz), 36.2, 26.5 (d, $^{3}J_{C\text{-}F}$ = 8.5 Hz), 19.7 (d, $^{4}J_{C\text{-}F}$ = 6.7 Hz), 11.3 (dd, $^{3}J_{C\text{-}F}$ = 5.5, 2.4 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -108.6 (d, ^{2}J = 239.9 Hz, 1F), -131.5 (dt, ^{2}J = 239.9, $^{3}J_{F\text{-}H}$ = 22.5 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3382, 2945, 1455, 1031, 988 cm^{-1}; HRMS (ESI): calcd for $C_8H_{18}F_2O_2N_1$, 198.1300 $[M+NH_4]^+$, found: 198.1300; MS (EI): *m/z* (%): 142 (7) $[M\text{-}2F]^+$; t_R (GC) = 8.96 minutes.

(1S,2S*,4S*)-3,3-difluoro-4-methylcyclohexane-1,2-diol (*1, 2-*cis*, 2, 4-*trans*-***4f***). Prepared according to general procedure B from **3f** (0.252 g, 1.00 mmol) with 1,3-*bis*(2,6-di*iso*propylphenyl-imidazol-2-ylidene)gold(I) chloride (5 mol %, 0.031 g) and silver hexafluoroantimonate(V) (5 mol %, 0.017 g) in dichloromethane (5.4 mL) and methanol (0.6 mL). After stirring for 21 hours at 40 °C the reaction was allowed to cool to room temperature and reduced with tetrabutylammonium borohydride (0.258 g, 1.00 mmol). The usual work up afforded a viscous pale yellow oil (0.294 g) which was purified by flash column chromatography (40 g silica, 15-25 % acetone in dichloromethane) to afford 1, 2-*cis*, 2, 4-*trans*-**4f** as a colourless solid (0.039 g). This material was purified further by recrystallization by vapour diffusion (methanol/pentane) to afford 1, 2-*cis*, 2, 4-*trans*-**4f** as a colourless plate (0.021 g, 11 %). m.p. = 118-120 °C; R_f = 0.42 (20 % acetone in dichloromethane); ^{1}H NMR (600 MHz, MeOD): δ = 3.84 (dt, J = 8.3, $J_{H\text{-}F}$ = 3.7 Hz, 1H), 3.71-3.61 (m, 1H), 2.22-2.06 (m, 1H), 1.77-1.68 (m, 1H), 1.68-1.59 (m, 2H), 1.18 (qd, $^{2}J = J$ = 13.5, J = 3.9 Hz, 1H), 1.01 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (150 MHz, MeOD): δ = 123.5 (dd, $^{1}J_{C\text{-}F}$ = 252.8, 242.5 Hz), 71.5 (dd, $^{2}J_{C\text{-}F}$ = 33.8, 21.6 Hz), 69.2 (d, $^{3}J_{C\text{-}F}$ = 7.6 Hz), 31.8 (t, $^{2}J_{C\text{-}F}$ = 22.0 Hz), 26.7 (d, $^{3}J_{C\text{-}F}$ = 8.4 Hz), 26.5, 10.4 (t, $^{3}J_{C\text{-}F}$ = 3.9 Hz) ppm; ^{19}F NMR (376 MHz, MeOD): δ = (-108.9) – (-109.9) (m, including -109.3 (app. d, ^{2}J = 250.3 Hz, 1F)), -124.5 (dd, ^{2}J = 250.3, $^{3}J_{F\text{-}H}$ = 29.6 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3400 (broad), 2963, 1457, 1046,

957 cm^{-1}; HRMS (APCI): calcd for $C_7H_{16}F_2O_2N$, 184.1144 $[M+NH_4]^+$, found: 184.1141; MS (CI): *m/z* (%): 184 (100) $[M+NH_4]^+$; t_R (GC) = 9.44 minutes.

(1S,2S*,4S*)-3,3-difluoro-4,6,6-trimethylcyclohexane-1,2-diol (*1, 2-*cis*, 2, 4-*trans*-***4g****)*. Prepared according to general procedure B from **3g** (0.280 g, 1.00 mmol) with 1,3-*bis*(2,6-di*iso*propylphenyl-imidazol-2-ylidene)gold(I) chloride (5 mol %, 0.031 g) and silver hexafluoroantimonate(V) (5 mol %, 0.017 g) in dichloromethane (5.4 mL) and methanol (0.6 mL). After stirring for 21 hours at 40 °C the reaction was allowed to cool to room temperature and reduced with tetrabutylammonium borohydride (0.258 g, 1.00 mmol). The usual work up afforded a viscous pale yellow oil (0.586 g) which was purified by flash column chromatography (40 g silica, 5 % acetone in dichloromethane) to afford 1, 2-*cis*, 2, 4-*trans*-**4g** as a colourless solid (0.123 g, 63 %). R_f = 0.25 (5 % acetone in dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.04 (tt, J_{H-F} = 6.6, J = 3.5 Hz, 1H), 3.49-3.38 (m, 1H), 2.46-2.24 (m, (including 2.39 (app. d, J =3.5 Hz, 1H) and 2.29 (d, J =9.6 Hz, 1H)), 1H), 1.43 (ddd, ^2J = 14.1, $^4J_{H-F}$ = 6.2, J = 4.2 Hz, 1H), 1.26 (br. t, ^2J = J = 14.1 Hz, 1H), 1.07 (s, 3H), 1.06 (d, J = 6.2 Hz, 3H), 1.03 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 122.8 (dd, $^1J_{C-F}$ = 251.1, 243.3 Hz), 74.2 (d, $^3J_{C-F}$ = 6.7 Hz), 71.5 (dd, $^2J_{C-F}$ = 36.3, 22.2 Hz), 41.6 (d, $^3J_{C-F}$ = 8.8 Hz), 34.8, 29.2, 28.8 (t, $^2J_{C-F}$ = 21.5 Hz), 19.9, 10.9 (t, $^3J_{C-F}$ = 3.7 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = (-109.0) – (-109.9) (m, including -109.4 (app. d, ^2J = 253.0 Hz, 1F)), -124.5 (dddd, ^2J = 253.0, $^3J_{F-H}$ = 28.9, 6.2, $^4J_{F-H}$ = 4.2 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3350, 2926, 1465,1371, 1005 cm^{-1}; HRMS (NSI-ES): calcd for $C_9H_{16}F_2O_2Na$, 217.1011 $[M+Na]^+$, found: 217.1012; MS (EI): *m/z* (%): 161(3) $[M-CH_3F]^+$, 102 (61) $[M-C_4H_6F_2]^+$, 72(100) $[M-C_6H_{12}F_2]^+$; t_R (GC) = 9.64 minutes; elemental analysis calcd (%) for $C_9H_{16}F_2O_2$: C, 55.66; H, 8.30; found**:** C, 55.35; H, 8.23.

(4S,5R*,7S*)-6,6-Difluoro-4,7-dimethylspiro[2.5]octane-4,5-diol (*4, 5-*trans*, 5, 7-*cis*-***4h****), (4S*,5R*,7R*)-6,6-difluoro-4,7-dimethylspiro[2.5]octane-4,5-diol (*4, 5-*trans*, 5, 7-

*trans-**4h**) and (4R*,5R*,7S*)-6,6-difluoro-4,7-dimethylspiro[2.5]octane-4,5-diol (*4, 5-*cis*, 5, 7-*cis-**4h**)*. Prepared according to general procedure B from **3h** (0.352 g, 1.21 mmol) with 1,3-*bis*(2,6-di*iso*propylphenyl-imidazol-2-ylidene)gold(I) chloride (5 mol %, 0.037 g) and silver hexafluoroantimonate(V) (5 mol %, 0.021 g) in dichloromethane (6.5 mL) and methanol (0.7 mL). After stirring for 18 hours at 40 °C the reaction was allowed to cool to room temperature and reduced with tetrabutylammonium borohydride (0.311 g, 1.21 mmol). The usual work up afforded a viscous pale yellow oil (0.564 g) which was purified by flash column chromatography (40 g silica, 6 % acetone in dichloromethane) to afford a mixture of 4, 5-*trans*, 5, 7-*cis*-**4h**, 4, 5-*trans*, 5, 7-*trans*-**4h** and 4, 5-*cis*, 5, 7-*cis*-**4h** (0.125 g). The material was further purified by flash column chromatography (40 g silica, 38 % ethyl acetate in hexane) to afford a mixture of 4, 5-*trans*, 5, 7-*cis*-**4h**, 4, 5-*trans*, 5, 7-*trans*-**4h** and 4, 5-*cis*, 5, 7-*cis*-**4h** (73.4 mg, 29 %, 1.3:1:0.1) as a pale yellow oil, 4, 5-*trans*, 5, 7-*cis* -**4h** as a pale yellow oil (13.8 mg, 6 %) and 4, 5-*trans*, 5, 7-*trans*-**4h** as a colourless solid (12.8 mg, 5 %). R_f 4, 5-*trans*, 5, 7-*cis*-**4h** = 0.52 (10 % acetone in dichloromethane); R_f 4, 5-*trans*, 5, 7-*trans*-**4h** = 0.61 (10 % acetone in dichloromethane); 4, 5-*cis*, 5, 7-*cis*-**4h** co eluted with the 4, 5-*trans*, 5, 7-*trans* diastereoisomer; The following signals were attributed to the major 4, 5-*trans*, 5, 7-*cis*-diastereoisomer **4h** and minor 4, 5-*trans*, 5, 7-*trans*-**4h** and 4, 5-*cis*, 5, 7-*cis*-diastereoisomers **4h** ^{1}H NMR (600 MHz, DMSO-d_6, 373 K): δ = 3.63-3.48 (m, 1H), 0.84-0.74 (m, 2H), 0.22-0.06 (m, 3H) ppm;

The following signals were attributed to the major 4, 5-*trans*, 5, 7-*cis*-diastereoisomer **4h** (assigned on the basis of δ and intensity); ^{1}H NMR (600 MHz, DMSO-d_6, 373 K): δ = 4.81 (br. s, 1H), 3.78 (br. s, 1H), 2.09-1.91 (m, 1H), 1.75 (br. t, $^2J = J$ = 13.4 Hz, 1H), 1.16 (d, $^5J_{H-F}$ = 2.2 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 0.91-0.84 (m, 1H), 0.59 (ddd, ^2J = 9.3, J = 5.7, 3.8 Hz, 1H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6, 373 K): δ = 123.8 (t, $^1J_{C-F}$ = 247.0 Hz), 77.5 (t, $^2J_{C-F}$ = 19.1 Hz), 72.2 (d, $^3J_{C-F}$ = 8.3 Hz), 37.8 (d, $^3J_{C-F}$ = 8.7 Hz), 36.7 (t, $^2J_{C-F}$ = 22.3 Hz),

25.6, 20.0 (d, $^{4}J_{C\text{-}F}$ = 5.6 Hz), 11.8, 8.5, 6.6 ppm; ^{19}F NMR (376 MHz, DMSO-*d*$_6$, 373 K): δ = -104.7 (dq, ^{2}J = 240.6, $^{3}J_{F\text{-}H}$ = $^{4}J_{F\text{-}H}$ = 4.9 Hz, 1F), -127.9 (dt, ^{2}J = 240.6, $^{3}J_{F\text{-}H}$ = 24.2 Hz, 1F) ppm;

The following signals were attributed to the minor 4, 5-*trans*, 5, 7-*trans*-diastereoisomer **4h** (assigned on the basis of δ and intensity); ^{1}H NMR (600 MHz, DMSO-*d*$_6$, 373 K): δ 4.90 (br. s, 1H), 3.75 (br. s, 1H), 2.37-2.21 (m, 1H), 1.57 (br. dd, ^{2}J = 13.9 , J = 8.0 Hz, 1H), 1.34-1.25 (m, 1H), 1.04 (d, J = 7.1 Hz, 3H), 1.02 (s, 3H), 0.55-0.48 (m, 1H) ppm; ^{13}C NMR (150 MHz, DMSO-*d*$_6$, 373 K): δ = 125.0 (t, $^{1}J_{C\text{-}F}$ = 248.1 Hz), 74.7 (t, $^{2}J_{C\text{-}F}$ = 22.5 Hz), 73.6, 36.8, 35.0 (t, $^{2}J_{C\text{-}F}$ = 22.2 Hz), 22.5, 21.0 (d, $^{4}J_{C\text{-}F}$ = 5.6 Hz), 13.4, 8.5, 7.9 ppm; ^{19}F NMR (376 MHz, DMSO-*d*$_6$, 373 K): δ = -106.7 (br. d, ^{2}J = 243.4 Hz, 1F), -110.1 (d, ^{2}J = 243.4 Hz, 1F) ppm;

The following signals were attributed to the minor 4, 5-*cis*, 5, 7-*cis*-diastereoisomer **4h** (assigned on the basis of δ and intensity); ^{1}H NMR (600 MHz, DMSO-*d*$_6$, 373 K): δ 0.99 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-*d*$_6$, 373 K): δ = 37.4 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz), 29.3, 12.1, 9.9, 8.2 ppm; ^{19}F NMR (376 MHz, DMSO-*d*$_6$, 373 K): δ = -103.2 (d, ^{2}J = 238.9 Hz, 1F), -127.0 (dt, ^{2}J = 238.9, $^{3}J_{F\text{-}H}$ = 26.5 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3427, 2933, 1465, 1026, 991 cm^{-1}; HRMS (APCI): calcd for $C_{10}H_{15}F_2O_1$, 189.1091 $[M\text{-}H_2O+H]^+$, found: 189.1089; MS (EI): *m/z* (%): 168 (12) $[M\text{-}2F]^+$ (major 4, 5-*trans*, 5, 7-*cis* diastereoisomer), 168 (21) $[M\text{-}2F]^+$ (minor 4, 5-*trans*, 5, 7-*trans* diastereoisomer), 168 (30) $[M\text{-}2F]^+$ (minor 4, 5-*cis*, 5, 7-*cis* diastereoisomer); t_R (GC) = 10.71 minutes (major 4, 5-*trans*, 5, 7-*cis* diastereoisomer), 10.84 minutes (minor 4, 5-*trans*, 5, 7-*trans* diastereoisomer), 11.00 (minor 4, 5-*cis*, 5, 7-*cis* diastereoisomer). Diastereomerically pure 4, 5-*trans*, 5, 7-*cis* **4h**: ^{1}H NMR (600 MHz, DMSO-*d*$_6$, 373 K): δ = 4.84 (br. d, J = 5.5 Hz, 1H), 3.81 (br. s, 1H), 3.51 (dt, $J_{H\text{-}F}$ = 24.2, 5.5, J = 5.5 Hz, 1H), 2.09-1.92 (m, 1H), 1.74 (br. t, ^{2}J = J = 13.6 Hz, 1H), 1.14 (d, $^{5}J_{H\text{-}F}$ = 2.2 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H), 0.90-0.83 (m, 1H), 0.79 (dt, ^{2}J = 13.6, $^{4}J_{H\text{-}F}$ = J = 4.6 Hz, 1H), 0.58 (ddd, ^{2}J = 9.3, J = 5.7, 3.8 Hz, 1H), 0.21-0.13 (m, 1H), 0.13-0.03 (m, 1H) ppm; ^{13}C

NMR (150 MHz, DMSO-d_6, 373 K): δ = 122.7 (dd, $^1J_{C\text{-}F}$ = 249.8, 244.8 Hz), 76.5 (t, $^2J_{C\text{-}F}$ = 19.4 Hz), 71.2 (d, $^3J_{C\text{-}F}$ = 9.0 Hz), 36.8 (d, $^3J_{C\text{-}F}$ = 9.0 Hz), 35.7 (t, $^2J_{C\text{-}F}$ = 21.9 Hz), 24.5, 19.0 (d, $^4J_{C\text{-}F}$ = 6.1 Hz), 10.8 (dd, $^3J_{C\text{-}F}$ = 5.8, 2.5 Hz), 7.4, 5.5 ppm; ^{19}F NMR (376 MHz, DMSO-d_6, 373 K): δ = -104.7 (app. dq, ^2J = 240.6, $^3J_{F\text{-}H}$ = $^4J_{F\text{-}H}$ = 4.9 Hz, 1F), -127.9 (dt, ^2J = 240.6, $^3J_{F\text{-}H}$ = 24.2 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3427, 2938, 1376, 1231, 1090, 991 cm^{-1}; HRMS (APCI): calcd for $C_{10}H_{20}F_2O_2N_1$, 224.1462 $[M+NH_4]^+$, found: 224.1458; MS (EI): *m/z* (%): 168 (12) $[M\text{-}2F]^+$; t_R (GC) = 10.71 minutes; Diastereomerically pure 4, 5-*trans*, 5, 7-*trans* **4h**: m.p. = 66-68 °C (recrystallized from chloroform/pentane as a colourless plate); ^{1}H NMR (600 MHz, DMSO-d_6, 373 K): δ 4.92 (br. d, J = 5.8 Hz, 1H), 3.77 (br. s, 1H), 3.51 (dt, $J_{H\text{-}F}$ = 15.2, 5.9, J = 5.9 Hz, 1H), 2.34-2.22 (m, 1H), 1.56 (br. dd, ^2J = 13.9 , J = 8.0 Hz, 1H), 1.29 (br. d, , ^2J = 13.9 Hz, 1H), 1.04 (d, J = 7.2 Hz, 3H), 1.01 (s, 3H), 0.76 (br. dt, ^2J = 9.1, J = 4.1 Hz, 1H), 0.54-0.48 (m, 1H), 0.17 (ddd, ^2J = 9.1, J = 5.5, 4.3 Hz, 1H), 0.13 (ddd, ^2J = 9.2, J = 5.2, 3.6 Hz, 1H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6, 373 K): δ = 124.0 (t, $^1J_{C\text{-}F}$ = 248.5 Hz), 73.6 (t, $^2J_{C\text{-}F}$ = 22.3 Hz), 72.5, 35.8 (t, $^3J_{C\text{-}F}$ = 3.9 Hz), 33.9 (t, $^2J_{C\text{-}F}$ = 21.9 Hz), 21.4, 20.0 (d, $^4J_{C\text{-}F}$ = 4.0 Hz), 12.4 (t, $^3J_{C\text{-}F}$ = 5.1 Hz), 7.4, 6.9 ppm; ^{19}F NMR (376 MHz, DMSO-d_6, 373 K): δ = -106.7 (br. d, ^2J = 243.4 Hz, 1F), -110.1 (d, ^2J = 243.4 Hz, 1F) ppm (the ^{19}F-^{1}H splitting was not resolved in the ^{19}F NMR spectrum); $\bar{\nu}$/(neat) = 3382, 2931, 1380, 1023, 824 cm^{-1}; HRMS (APCI): calcd for $C_{10}H_{15}F_2O_1$, 189.1091 $[M\text{-}H_2O+H]^+$, found: 189.1087; MS (EI): *m/z* (%): 168 (21) $[M\text{-}2F]^+$; t_R (GC) = 10.84 minutes.

(6R,7S*,9S*)-8,8-Difluoro-6,9-dimethylspiro[4.5]decane-6,7-diol (*6, 7-*trans*, 7, 9-*trans*-**4i**) and (6S*,7S*,9S*)-8,8-difluoro-6,9-dimethylspiro[4.5]decane-6,7-diol (*6, 7-*cis*, 7, 9-*trans*-**4i**)*. Prepared according to general procedure B from **3i** (0.339 g, 1.06 mmol) with 1,3-*bis*(2,6-di*iso*propylphenyl-imidazol-2-ylidene)gold(I) chloride (5 mol %, 0.033 g) and silver hexafluoroantimonate(V) (5 mol %, 0.018 g) in dichloromethane (5.4 mL) and

methanol (0.6 mL). After stirring for 2 hours at 40 °C the reaction was allowed to cool to room temperature and reduced with tetrabutylammonium borohydride (0.273 g, 1.06 mmol). The usual work up afforded a viscous pale yellow oil (0.395 g). The crude material was purified by flash column chromatography (40 g silica, 6% acetone in dichloromethane) to afford a mixture of 6, 7-*trans*, 7, 9-*trans*-**4i**, and 6, 7-*cis*, 7, 9-*trans*-**4i** (0.168 g). The material was further purified by flash column chromatography (40 g silica, 6 % acetone in dichloromethane) to afford an inseparable mixture of 6, 7-*trans*, 7, 9-*trans*-**4i**, and 6, 7-*cis*, 7, 9-*trans*-**4i** (0.108 g, 44 %, 3.8:1). R_f = 0.7 (8 % acetone in dichloromethane); The following signals were attributed to both the minor 6, 7-*cis*, 7, 9-*trans*-diastereoisomer **4i** and major 6, 7-*trans*, 7, 9-*trans*-diastereoisomer **4i** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.48-2.13 (m, including 2.23 (br.s, 1H), 1H), 2.04-1.38 (envelope, 13H), 1.37-1.22 (m, including 1.33 (s, 3H), 6H) ppm; The following signals were attributed to the major 6, 7-*trans*, 7, 9-*trans*-diastereoisomer **4i** (assigned on the basis of δ and intensity); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.64 (t, J_{H-F} = 5.8 Hz, 1H), 2.23 (br. s, 1H), 1.33 (s, 3H), 1.07 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, MeOD): δ = 127.1 (t, $^1J_{C-F}$ = 247.7 Hz), 79.8 (d, $^3J_{C-F}$ = 5.3 Hz), 79.2 (dd, $^2J_{C-F}$ = 27.8, 20.7 Hz), 52.0, 43.2 (d, $^3J_{C-F}$ = 8.0 Hz), 38.8, 36.8, 33.5 (t, $^2J_{C-F}$ = 21.5 Hz), 29.7, 27.4, 24.4, 14.3 (d, $^3J_{C-F}$ = 4.3 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -107.6 (d, ^2J = 253.2 Hz, 1F), -116.2 (dd, ^2J = 253.2, $^3J_{F-H}$ = 28.7 Hz, 1F) ppm (the ^{19}F-^{1}H splitting was not resolved in the ^{19}F NMR spectrum); The following signals were attributed to the minor 6, 7-*cis*, 7, 9-*trans*-diastereoisomer **4i** (assigned on the basis of δ and intensity); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.67 (t, J_{H-F} = 6.6 Hz, 1H), 2.69 (br. s, 1H), 2.65 (br. s, 1H) 1.26 (d, $^5J_{H-F}$ = 4.1 Hz, 3H), 1.05 (d, J = 6.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, MeOD): δ = 126.9 (dd, $^1J_{C-F}$ = 248.7, 243.0 Hz), 80.5 (dd, $^2J_{C-F}$ = 32.9, 20.4 Hz), 76.7 (d, $^3J_{C-F}$ = 6.9 Hz), 52.9, 41.4 (d, $^3J_{C-F}$ = 8.7 Hz), 38.2, 33.6, 33.0 (t, $^2J_{C-F}$ = 21.8 Hz), 28.0, 25.4, 25.3 (d, $^4J_{C-F}$ = 8.4 Hz), 13.9 (d, $^3J_{C-F}$ = 5.4 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ -105.9 (dq, ^2J = 253.7, $^3J_{F-H}$ = $^4J_{F-H}$ =

5.4 Hz, 1F), -117.5 (dd, ^{2}J = 253.7, $^{3}J_{F\text{-}H}$ = 28.9 Hz, 1F) ppm (the 6.6 Hz ^{19}F-^{1}H splitting was not resolved in the ^{19}F NMR spectrum); $\bar{\nu}$/(neat) = 3600, 3331, 2947, 1454, 1383, 1086, 978 cm^{-1}; HRMS (APCI): calcd for $C_{12}H_{22}F_2O_2N_1$, 252.1770 $[M\text{-}H]^+$, found: 252.1769; MS (EI): *m/z* (%): 219 (1) $[M\text{-}CH_3]^+$; t_R (GC) = 12.17 minutes;* elemental analysis calcd (%) for $C_{12}H_{20}F_2O_2$: C, 61.52; H, 8.60; found**:** C, 61.76; H, 8.64. This analysis was obtained for the amorphous solid obtained following chromatography so no melting point was recorded. * the individual diastereoisomers appeared as one peak by GC-MS.

Cis-methyl (3S,4aR*)-3-methoxy-3-methyl-4,4a,5,6,7,8-hexahydro-3H-isochromene-1-carboxylate (*3, 4a-*cis*-**5***) and trans-methyl (3R*,4aR*)-3-methoxy-3-methyl-4,4a,5,6,7,8-hexahydro-3H-isochromene-1-carboxylate (*3, 4a-*trans*-**5***)*. Prepared according to general procedure B from *trans*-**3j** and *cis*-**3j** (0.253 g, 0.83 mmol) with 1,3-*bis*(2,6-di*iso*propylphenyl-imidazol-2-ylidene)gold(I) chloride (5 mol %, 0.026 g) and silver hexafluoroantimonate(V) (5 mol %, 0.014 g) in dichloromethane (4.5 mL) and methanol (0.5 mL). After stirring for 15 minutes at 40 °C the reaction was allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue taken up in ethyl acetate (20 mL). The organics were washed with saturated aqueous sodium bicarbonate (15 mL). The aqueous layer was further extracted with ethyl acetate (3 x 15 mL) and the organics combined, dried over magnesium sulphate and concentrated under reduced pressure to afford the crude product as a dark orange oil (0.204 g). The crude material was purified by flash column chromatography using a Thomson Single Step cartridge (12 g silica, 0-5 % acetone in dichloromethane) to afford an inseparable mixture of 3, 4a-*cis* **5**, and 3, 4a-*trans*-**5** as a pale yellow oil. After storing the material in the freezer at 0 °C for one year the material solidified to afford a pale yellow solid (0.057 g, 29 %, 7.3:1). m.p. = 40-42 °C (crystals were grown by slow evaporation from chloroform/pentane under reduced pressure as small colourless prisms); R_f = 0.54 (10 % ethyl acetate in hexane);The following signals were

attributed to both the minor 3, 4a-*trans*-diastereoisomer **5** and major 3, 4a-*cis*-diastereoisomer **5** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.79 (s, 3H), 3.53-3.42 (m, 1H), 1.97-1.61 (envelope, 5H), 1.47 (s, 3H), 1.45-1.22 (m, 4H) ppm; The following signals were attributed to the major 3, 4a-*cis*-diastereoisomer **5** (assigned on the basis of δ and intensity); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.25 (s, 3H), 2.35-2.22 (m, 1H), 2.00 (dd, ^{2}J = 13.7, 7.0 Hz, 1H), 1.07 (dq, $^{2}J = J$ = 12.5, J = 3.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2, 132.7, 128.7, 97.1, 51.2, 48.6, 40.2, 33.3, 31.7, 27.1, 26.2, 25.1, 22.2 ppm; The following signals were attributed to the minor 3, 4a-*trans*-diastereoisomer **5** (assigned on the basis of δ and intensity); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.31 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.1, 132.9, 128.5, 98.3, 51.2, 48.4, 37.6, 34.6, 34.4, 28.1, 27.3, 26.0, 21.8 ppm; $\bar{\nu}$/(neat) = 2921, 1719, 1435, 1279, 1115, 1045, 881 cm^{-1}; HRMS (APCI): calcd for $C_{13}H_{24}O_4N_1$, 258.1700 $[M+NH_4]^+$, found: 258.1701; MS (EI): *m/z* (%): 240 (1) $[M]^+$ (3, 4a-*cis* and 3, 4a-*trans* diastereoisomers); t_R (GC) = 12.19 minutes (major 3, 4a-*cis* diastereoisomer), 12.26 minutes (minor 3, 4a-*trans* diastereoisomer).

General Procedure C: Propargyl Ether Preparation. *1,1-Difluoro-2-([methoxyethoxy]- methoxy) 3-(Propargyloxy)hexane (**6a**)*. Propargyl ether **6a** was prepared according to the procedure of Percy and co-workers.[15] Propargyl bromide (0.78 mL of an 80 wt % solution in toluene, 7.0 mmol) was added dropwise to a vigorously stirred mixture of allylic alcohol **3k** (1.54g, 5.4 mmol) and tetra(*n*-butyl)ammonium hydrogen sulfate (0.085 g, 0.25 mmol) in aqueous sodium hydroxide (4.5 mL, 50 wt %) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 18 hours. The mixture was quenched with aqueous saturated ammonium chloride (20 mL) and transferred to a separating funnel. Water (10 mL) was added and the product was extracted with diethyl ether (4 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude product as a yellow oil (1.91 g). The crude propargyl

ether was purified by flash column chromatography (90 g cartridge, 20 % diethyl ether in hexane) to afford **6a** as a colourless oil (1.23 g, 71 %). R_f = 0.62 (50 % diethyl ether in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.04 (d, ^2J = 6.2 Hz, 1H), 4.95 (d, ^2J = 6.2 Hz, 1H), 4.28-4.18 (m, including 4.22 (dd, ^2J = 15.7, ^4J = 2.2 Hz, 1H), 1H), 4.09 (dd, ^2J = 15.7, ^4J = 2.2 Hz, 1H), 3.94-3.76 (m, 1H), 3.59 (t, J = 4.9 Hz, 2H), 3.41 (s, OCH_3, 3H), 3.42 (t, ^4J = 2.2 Hz, 1H), 1.86-1.61 (m, 2H), 1.50-1.20 (m, 8H), 0.90 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7 (dd, $^1J_{C\text{-}F}$ = 295.0, 285.5 Hz), 111.4 (dd, $^2J_{C\text{-}F}$ = 36.3. 10.5 Hz), 96.4 (t, $^4J_{C\text{-}F}$ = 3.3 Hz), 78.9, 73.7, 73.6 (t, $^4J_{C\text{-}F}$ = 3.0 Hz), 71.1, 67.8, 58.4, 54.9, 31.1, 28.4, 24.8, 22.0, 13.5 ppm; ^{19}F (376 MHz, $CDCl_3$): δ = -96.9 (d, ^2J = 62.3 Hz, 1F), -109.0 (d, ^2J = 62.3 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3309, 2924, 1747, 1236, 1074, 955 cm^{-1}; HRMS (ESI): calcd for $C_{16}H_{30}F_2O_4N_1$, 338.2137 $[M+NH_4]^+$, found: 338.2139; MS (CI): *m/z* (%): 281 (1) $[M\text{-}C_3H_3]^+$, 265 (4) $[M\text{-}C_3H_3O]^+$, 245 (6) $[M\text{-}C_3H_7O_2]^+$, 153 (4) $[C_{10}H_{17}O]^+$, 89 (78) $[C_4H_9O_2]^+$, 59 (100) $[C_3H_7O]^+$; t_R (GC) = 12.76 minutes.

*1,1-Difluoro-2-([methoxyethoxy]- methoxy) 3-(Propargyloxy)-cyclohexane (**6b**)*. Prepared as for **6a** from allylic alcohol **3k** (2.24 g, 8.40 mmol), propargyl bromide (1.15 mL of an 80 wt % solution in toluene, 9.9 mmol) and tetra(*n*-butyl)ammonium hydrogen sulfate (0.126 g, 0.34 mmol) in aqueous sodium hydroxide (6.6 mL, 50 wt %) at 0 °C. The crude ether (2.39 g) was purified by flash column chromatography (90 g cartridge, 15 % diethyl ether in hexane) to afford **6b** as a colourless oil (1.72 g, 68 %). R_f = 0.42 (30 % diethyl ether in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.02 (d, ^2J = 6.4 Hz, 1H), 4.92 (d, ^2J = 6.4 Hz, 1H), 4.20 (dd, ^2J = 15.7, ^4J = 2.4 Hz, 1H), 4.05 (dd, ^2J = 15.7, ^4J = 2.4 Hz, 1H), 3.92-3.83 (m, 2H), 3.82-3.73 (m, 1H), 3.57 (t, J = 4.9 Hz, 2H), 3.39 (s, 3H,), 2.39 (t, ^4J = 2.4 Hz, 1H), 2.10 (br. d, ^2J = 13.7 Hz, 1H), 1.86-1.52 (m, 5H), 1.37-1.09 (m, 3H), 1.07-0.82 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.2 (dd, $^1J_{C\text{-}F}$ = 295.5, 284.9 Hz), 110.5 (dd, $^2J_{C\text{-}F}$ = 36.3.

10.0 Hz), 96.4 (t, $^{4}J_{C\text{-}F}$ = 3.2 Hz), 79.1, 78.4 (t, $^{3}J_{C\text{-}F}$ = 3.5 Hz), 73.6, 71.1, 67.8, 58.5, 55.2, 38.2, 29.2, 28.2, 25.9, 25.2, 25.1 ppm; ^{19}F (376 MHz, $CDCl_3$): δ = -96.8 (d, ^{2}J = 63.7 Hz, 1F), -109.6 (d, ^{2}J = 63.7 Hz, 1F) ppm; ν̄/(neat) = 3305, 2921, 1745, 1232, 1045, 957 cm^{-1}; HRMS (APCI): calcd for $C_{16}H_{28}F_2O_4N_1$, 336.1986 $[M+NH_4]^+$, found: 336.1981; MS (EI): *m/z* (%): 243 (3) $[M\text{-}C_3H_7O_2]^+$, 187 (25) $[M\text{-}C_7H_{15}O_2]^+$, 89 (71) $[C_4H_9O_2]^+$, 59 (100) $[C_3H_7O]^+$; t_R (GC) = 13.04 minutes.

*1,1-Difluoro-2-([methoxyethoxy]- methoxy) 3-(Propargyloxy)- tetrahydro-2H-pyran-4-yl (**6c**)*. Prepared as for **6a** from allylic alcohol **3m** (1.84 g, 6.5 mmol), propargyl bromide (1.00 mL of an 80 wt % solution in toluene, 8.5 mmol) and tetra(*n*-butyl)ammonium hydrogen sulfate (0.107 g, 0.29 mmol) in aqueous sodium hydroxide (5.3 mL, 50 wt %) at 0 °C. The crude ether (2.22 g) was purified by flash column chromatography (90 g cartridge, 50 % diethyl ether in hexane) to afford **6c** as a pale yellow oil (1.82 g, 88 %). R_f = 0.32 (50 % diethyl ether in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.01 (d, ^{2}J = 6.6 Hz, 1H), 4.93 (d, ^{2}J = 6.6 Hz, 1H), 4.26-4.17 (m, 1H), 4.10-4.03 (m, 1H), 4.02-3.82 (m, 4H), 3.82-3.73 (m, 1H), 3.56 (t, *J* = 5.1 Hz, 2H), 3.42-3.32 (m, 5H), 2.41 (t, ^{4}J = 2.3 Hz, 1H), 2.04-1.90 (m, 2H), 1.55-1.45 (m, 1H), 1.44-1.17 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.3 (dd, $^{1}J_{C\text{-}F}$ = 294.9, 285.3 Hz), 110.0 (dd, $^{2}J_{C\text{-}F}$ = 36.5, 10.3 Hz), 96.5 (t, $^{4}J_{C\text{-}F}$ = 3.4 Hz), 78.8, 77.8 (t, $^{3}J_{C\text{-}F}$ = 3.6 Hz), 73.9, 71.1, 67.8, 67.1, 66.8, 58.5, 55.2, 35.7, 29.5, 28.0 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -95.9 (d, ^{2}J = 61.6 Hz, 1F), -108.9 (d, ^{2}J = 61.6 Hz, 1F) ppm; ν̄/(neat) = 3263, 2915, 1745, 1229, 1046, 948 cm^{-1}; HRMS (ESI): calcd for $C_{15}H_{26}F_2O_5N_1$, 338.1774 $[M+NH_4]^+$, found: 338.1775; MS (EI): *m/z* (%): 281 (1) $[M\text{-}C_3H_3]^+$, 89 (100) $[C_4H_9O_2]^+$, 59 (96) $[C_3H_7O]^+$; t_R (GC) = 13.36 minutes.

*1,1-difluoro-2-([methoxyethoxy]- methoxy) 3-(Propargyloxy)- phenyl (**6d**)*. Prepared as for **6a** from allylic alcohol **3n** (1.90 g, 6.9 mmol), propargyl bromide (1.00 mL of an 80 wt % solution in toluene, 9.0 mmol) and tetra(*n*-butyl)ammonium hydrogen sulfate (0.107 g,

0.31 mmol) in aqueous sodium hydroxide (5.6 mL, 50 wt %) at 0 °C. The crude ether (2.14 g) was purified by flash column chromatography (90 g cartridge, 25 % diethyl ether in hexane) to afford **6d** as a pale yellow oil (1.71 g, 79 %). R_f = 0.27 (20 % diethyl ether in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47- 7.29 (m, 5H), 5.46 (t, $^4J_{H\text{-}F}$ = 3.5 Hz, 1H), 4.96 (d, ^2J = 6.4 Hz, 1H), 4.86 (d, ^2J = 6.4 Hz, 1H), 4.28 (t, ^4J = 2.4 Hz, 2H), 3.79-3.67 (m, 1H), 3.53 (t, J = 4.6 Hz, 2H), 3.39 (s, 3H), 2.48 (t, ^4J = 2.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6 (dd, $^1J_{C\text{-}F}$ = 294.3, 287.7 Hz), 136.7, 127.9, 127.6, 126.2, 112.7 (dd, $^2J_{C\text{-}F}$ = 35.4, 11.9 Hz), 96.7 (t, $^4J_{C\text{-}F}$ = 3.2 Hz), 78.5, 74.5, 74.4 (app. d, $^3J_{C\text{-}F}$ = 2.5 Hz), 71.0, 67.8, 58.5, 55.2 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -96.8 (d, ^2J = 59.8 Hz, 1F), -107.8 (dd, ^2J = 59.8, $^4J_{F\text{-}H}$ = 3.5 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3284, 2920, 1746, 1231, 1054, 954 cm^{-1}; HRMS (APCI): calcd for $C_{16}H_{22}F_2O_4N_1$, 330.1517 $[M+NH_4]^+$, found: 330.1520; MS (EI): *m/z* (%): 145 (3) $[C_{10}H_9O]^+$, 89 (92) $[C_4H_9O_2]^+$, 59 (100) $[C_3H_7O]^+$; t_R (GC) = 13.42 minutes.

*1,1-Difluoro-2-([methoxyethoxy]- methoxy) 3 - (Propargyloxy)- 4-(trifluoromethyl)phenyl (**6e**)*. Prepared as for **6a** from allylic alcohol **3o** (0.813 g, 2.4 mmol), propargyl bromide (0.35 mL of an 80 wt % solution in toluene, 3.0 mmol) and tetra(*n*-butyl)ammonium hydrogen sulfate (0.037 g, 0.10 mmol) in aqueous sodium hydroxide (3.0 mL, 50 wt %) at 0 °C. The crude ether (0.917 g) was purified by flash column chromatography (90 g cartridge, 20 % diethyl ether in hexane) to afford **6e** as a colourless oil (0.679 g, 74 %). R_f = 0.49 (5 % acetone in dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 5.51 (br. t, $^4J_{H\text{-}F}$ = 2.7 Hz, 1H), 4.97 (d, ^2J = 6.2 Hz, 1H), 4.79 (d, ^2J = 6.2 Hz, 1H), 4.31 (d, ^4J = 2.5 Hz, 2H), 3.75-3.69 (m, 2H), 3.55-3.49 (m, 2H), 3.39 (s, 3H), 2.49 (t, ^4J = 2.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7 (dd, $^1J_{C\text{-}F}$ = 294.6, 287.0 Hz), 140.9, 129.8 (q, $^2J_{C\text{-}F}$ = 32.8 Hz), 126.5, 124.8 (q, $^3J_{C\text{-}F}$ = 3.5 Hz), 123.7 (q, $^1J_{C\text{-}F}$ = 272.7 Hz), 112.0 (dd, $^2J_{C\text{-}F}$ = 36.0, 11.3 Hz), 96.7 (t, $^4J_{C\text{-}F}$ = 3.3 Hz), 78.0, 74.8, 73.9 (t, $^3J_{C\text{-}F}$ = 3.2 Hz), 70.9, 67.9, 58.5, 55.4 ppm; ^{19}F NMR (376 MHz,

$CDCl_3$): δ = -62.6 (s, 3F), -95.8 (d, ^2J = 58.7 Hz, 1F), -107.3 (dd, ^2J = 58.7, $^4J_{F\text{-}H}$ = 3.4 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3305, 2921, 1747, 1325, 1112, 1067, 1019 cm^{-1}; HRMS (APCI): calcd for $C_{17}H_{21}F_5O_4N_1$, 398.1385 $[M+NH_4]^+$, found: 398.1383; MS (EI): *m/z* (%): 361 (1) $[M\text{-}F]^+$, 213 (4) $[M\text{-}C_7H_{10}F_3O]^+$, 89 (96) $[C_4H_9O_2]^+$, 59 (100) $[C_3H_7O]^+$; t_R (GC) = 13.00 minutes.

*1,1-Difluoro-2-([methoxyethoxy]- methoxy) 3-(Propargyloxy)- 4-(methoxy)phenyl **(6f)***. Prepared as for **6a** from allylic alcohol **3p** (2.22 g, 7.3 mmol), propargyl bromide (1.06 mL of an 80 wt % solution in toluene, 9.0 mmol) and tetra(*n*-butyl)ammonium hydrogen sulfate (0.113 g, 0.31 mmol) in aqueous sodium hydroxide (6.0 mL, 50 wt %) at 0 °C. The crude ether (2.73 g) was purified by flash column chromatography (90 g cartridge, 50 % diethyl ether in hexane) to afford **6f** as a pale yellow oil (2.19 g, 88 %). R_f = 0.39 (50 % diethyl ether in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 5.51-5.37 (t, $^4J_{H\text{-}F}$ = 3.2 Hz, 1H), 4.96 (d, ^2J = 6.3 Hz, 1H), 4.76 (d, ^2J = 6.3 Hz, 1H), 4.24, 4.21 (dABq, J_{AB} = 15.9, ^4J = 2.4 Hz, 2H), 3.81 (s, 3H), 3.77-3.72 (m, 2H), 3.53 (t, *J* = 4.9 Hz, 2H), 3.38 (s, 3H), 2.47 (t, ^4J = 2.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 155.5 (dd, $^1J_{C\text{-}F}$ = 294.1, 286.1 Hz), 128.7, 127.5, 113.3, 112.8 (dd, $^2J_{C\text{-}F}$ = 34.6, 10.7 Hz), 96.7 (t, $^4J_{C\text{-}F}$ = 3.5 Hz), 78.5, 74.4, 74.1 (t, $^3J_{C\text{-}F}$ = 3.2 Hz), 71.0, 67.8, 58.5, 55.0, 54.7 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -97.2 (d, ^2J = 60.1 Hz, 1F), -107.9 (d, ^2J = 60.1, $^4J_{F\text{-}H}$ = 3.2 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3283, 2898, 1745, 1513, 1247, 1054, 955 cm^{-1}; HRMS (ESI): calcd for $C_{17}H_{24}F_2O_5N_1$, 360.1617 $[M+NH_4]^+$, found: 360.1620; MS (EI): *m/z* (%): 198 (19) $[M\text{-}C_7H_{12}O_3]^+$, 89 (76) $[C_4H_9O_2]^+$, 59 (100) $[C_3H_7O]^+$; t_R (GC) = 14.55 minutes.

General Procedure D: Difluorinated Pyran Preparation. *4,4-Difluoro-2-hexyl-5-methylenedihydro-2H-pyran-3(4H)-one **(7a)** and 3,3-dihydroxy-4,4-difluoro-2-hexyl-5-methylenedihydro-2H-pyran **(8a)***. 1,3-*bis*(2,6-di*iso*propylphenyl-imidazol-2-ylidene)gold(I) chloride (5 mol %, 0.031 g) and silver hexafluoroantimonate(V) (5 mol %,

0.017 g) were added to a round bottom flask. 2-Methyltetrahydrofuran (5 mL) was added and the solution stirred at room temperature (25 °C). During stirring, an off-white precipitate formed. The solution was stirred at room temperature then a solution of ether **6a** (0.320 g, 1 mmol) in 2-methyltetrahydrofuran (1 mL) was added in a stream *via* syringe. The mixture was stirred for 21 hours at room temperature then concentrated under reduced pressure to afford the crude product as a viscous dark brown oil (0.312 g). The crude material was purified by flash column chromatography (40 g silica, 3 % acetone in dichloromethane) to afford an inseparable mixture of ketone **7a** and hydrate **8a** as a colourless solid (0.163 g, 65 %, 1:1). A small sample of crystalline hydrate **8a** was prepared by recrystallization of the mixture by vapour diffusion using chloroform/pentane (8 mg, 3 %). m.p. = 70-72 °C (recrystallized from chloroform/pentane as small colourless needles); R_f = 0.57 (10 % acetone in dichloromethane); The following signals were attributed to both ketone **7a** and hydrate **8a** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.00-1.19 (envelope, 20H), 0.90 (t, J = 7.0 Hz, 6H) ppm; The following signals were attributed to ketone **7a** (assigned on comparison of the ^{1}H NMR spectrum of crystalline hydrate **8a** grown from chloroform/pentane with the ^{1}H NMR spectrum of the mixture and 2D NMR data); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.79 (br. d, $^4J_{H\text{-}F}$ = 4.0 Hz, 1H), 5.59 (app. q, $^4J_{H\text{-}F}$ = ^4J = 1.4 Hz, 1H), 4.54 (br. d, ^2J = 13.8 Hz, 1H), 4.42 (br. d, ^2J = 13.8 Hz, 1H), 4.17-4.10 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.7 (dd, $^2J_{C\text{-}F}$ = 27.9, 22.9 Hz), 138.1 (t, $^2J_{C\text{-}F}$ = 18.9 Hz), 116.9 (t, $^3J_{C\text{-}F}$ = 7.5 Hz), 109.9 (dd, $^1J_{C\text{-}F}$ = 261.2, 246.0 Hz), 81.3 (d, $^3J_{C\text{-}F}$ = 2.9 Hz), 67.8 (d, $^3J_{C\text{-}F}$ = 3.3 Hz), 31.2, 28.7, 25.3, 24.4, 22.1, 13.5 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -105.6 (d, ^2J = 265.6 Hz, 1F), -120.0 (d, ^2J = 265.6 Hz, 1F) ppm (the ^{19}F-^{1}H splittings are not resolved in the 376 MHz ^{19}F NMR spectrum). The following signals were attributed to hydrate **8a** (See page 162 of Results and Discussion); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.67 (d, $^4J_{H\text{-}F}$ = 4.9 Hz, 1H), 5.39 (app. q, $^4J_{H\text{-}F}$ = ^4J = 1.8 Hz, 1H), 4.32 (dd, ^2J = 12.9, $^4J_{H\text{-}F}$ = 4.2 Hz, 1H), 4.17 (br. d, ^2J = 12.9

Hz, 1H), 3.65-3.50 (m, 1H), 3.13 (br. s, 1H), 3.02 (br. s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.4 (t, $^2J_{C\text{-}F}$ = 20.5 Hz), 115.5 (dd, $^1J_{C\text{-}F}$ = 261.1, 244.3 Hz), 115.2 (t, $^3J_{C\text{-}F}$ = 7.0 Hz), 92.7 (dd, $^2J_{C\text{-}F}$ = 27.5, 20.1 Hz), 79.4 (d, $^3J_{C\text{-}F}$ = 2.9 Hz), 68.7 (d, $^3J_{C\text{-}F}$ = 4.4 Hz), 31.1, 28.8, 28.5, 26.0, 22.0, 13.5 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -107.7 (d, ^2J = 240.6 Hz, 1F), -138.7 (d, ^2J = 240.6 Hz, 1F) ppm; (the ^{19}F-^{1}H splittings are not resolved in the 376 MHz ^{19}F NMR spectrum); $\bar{\nu}$/(neat) = 3387, 2922, 1470, 1242, 1085, 933 cm^{-1}; HRMS (APCI): calcd for $C_{12}H_{19}F_2O_2$, 233.1353 $[M+H]^+$, found: 233.1352;* MS (EI): *m/z* (%): 232 (1) $[M]^+$, 119 (32) $[M\text{-}C_7H_{13}O]^+$,** t_R (GC) = 11.22 minutes.** *accurate mass was calculated for the ketone component of the mixture. **the mixture appeared as one peak by GC-MS, masses corresponded to that of the ketone.

*2-Cyclohexyl-4,4-difluoro-5-methylenedihydro-2H-pyran-3(4H)-one (**7b**) and 3,3-dihydroxy-2-cyclohexyl-4,4-difluoro-5-methylenedihydro-2H-pyran (**8b**)*. Ketone **7b** and hydrate **8b** were prepared according to general procedure D from propargyl ether **6b** (0.318 g, 1.00 mmol) with 1,3-*bis*(2,6-di*iso*propylphenyl-imidazol-2-ylidene)gold(I) chloride (5 mol %, 0.031 g) and silver hexafluoroantimonate(V) (5 mol %, 0.017 g) in 2-methyltetrahydrofuran (6.0 mL). The crude material (0.369 g) was purified by flash column chromatography (40 g silica, 5 % acetone in dichloromethane) to afford an inseparable mixture of ketone **7b** and hydrate **8b** as a colourless solid (0.145 g, 63 %, 7.3:1). R_f = 0.46 (5 % acetone in dichloromethane); The following signals were attributed to both ketone **7b** and hydrate **8b** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15-1.89 (m, 1H), 1.89-1.55 (m, 5H), 1.47-1.09 (m, 5H) ppm; The following signals were attributed to ketone **7b** (assigned on the basis of δ and intensity) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82-5.74 (m, 1H), 5.47 (br. s, 1H), 4.60 (app. dt, ^2J = 14.0, ^4J = 1.4 Hz, 1H), 4.37 (app. dquint, ^2J = 14.0, ^4J = $^4J_{H\text{-}F}$ = 1.4 Hz, 1H), 3.91 (dt, J = 5.0, $^4J_{H\text{-}F}$ = 2.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.1 (t, $^2J_{C\text{-}F}$ = 25.1 Hz), 137.9 (t, $^2J_{C\text{-}F}$ = 18.7 Hz), 116.8 (t, $^3J_{C\text{-}F}$ = 7.5 Hz), 109.6 (dd, $^1J_{C\text{-}F}$ = 257.0, 250.5

Hz), 85.7, 67.5, 37.8, 28.7, 26.6, 25.6 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -111.7 (dt, ^2J = 265.4, $^4J_{F\text{-}H}$ = 2.7 Hz, 1F), -120.0 (dq, ^2J = 265.4, $^4J_{F\text{-}H}$ = 2.9 Hz, 1F) ppm; The following signals were attributed to hydrate **8b** (assigned on the basis of δ and intensity) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.65 (d, $^4J_{H\text{-}F}$ = 4.9 Hz, 1H), 5.37 (app. q, $^4J_{H\text{-}F}$ = ^4J = 1.9 Hz, 1H), 4.33 (dd, ^2J = 12.9, $^4J_{H\text{-}F}$ = 4.2 Hz, 1H), 4.13 (br. d, ^2J = 12.9 Hz, 1H), 3.37-3.32 (m, 1H), 3.24 (br. s, 1H), 3.08 (br. s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.5 (t, $^2J_{C\text{-}F}$ = 20.6 Hz), 115.6 (dd, $^1J_{C\text{-}F}$ = 259.9, 244.8 Hz), 115.1 (t, $^3J_{C\text{-}F}$ = 7.0 Hz), 93.9 (dd, $^2J_{C\text{-}F}$ = 26.6, 20.1 Hz), 82.5 (d, $^3J_{C\text{-}F}$ = 1.7 Hz), 69.0 (d, $^3J_{C\text{-}F}$ = 4.4 Hz), 36.2, 30.9, 27.6, 25.4 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -107.1 (d, ^2J = 240.6 Hz, 1F), -139.4 (d, ^2J = 240.6 Hz, 1F) ppm (the ^{19}F-^{1}H splittings are not resolved in the 376 MHz ^{19}F NMR spectrum); $\bar{\nu}$/(neat) = 3404, 2917, 1452, 1217, 1091, 935 cm^{-1}; HRMS (APCI): calcd for $C_{12}H_{20}F_2O_2N_1$, 248.1457 $[M+NH_4]^+$, found: 248.1459;* MS (EI): *m/z* (%): 230 (2) $[M]^+$, 202 (58) $[M\text{-}C_2H_4]^+$,** t_R (GC) = 11.41 minutes.** *accurate mass was calculated for the ketone component of the mixture.**the mixture appeared as one peak by GC-MS, masses corresponded to that of the ketone.

3,3-Dihydroxy-4,4-difluoro-5-methylenehexahydro-2H,2'H-[2,4'-bipyran] ***(8c)***.

Hydrate **8c** was prepared according to general procedure D from propargyl ether **6c** (0.320 g, 1.00 mmol) with 1,3-*bis*(2,6-di*iso*propylphenyl-imidazol-2-ylidene)gold(I) chloride (5 mol %, 0.031 g) and silver hexafluoroantimonate(V) (5 mol %, 0.017 g) in 2-Methyltetrahydrofuran (6.0 mL). The crude material (0.393 g) was purified by flash column chromatography (40 g silica, 15 % acetone in dichloromethane) to afford hydrate **8c** as a colourless solid (0.154 g, 62 %). m.p. = 102-104 °C (recrystallized from tetrahydrofuran/pentane by vapour diffusion as a colourless needles); R_f = 0.35 (20 % acetone in dichloromethane); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.36 (s, 1H), 6.03 (s, 1H), 5.41 (d, $^4J_{H\text{-}F}$ = 4.90 Hz, 1H), 5.34 (br. s, 1H), 4.30 (dd, ^2J = 12.9, $^4J_{H\text{-}F}$ = 4.2 Hz, 1H), 3.94 (d, ^2J = 12.9 Hz, 1H), 3.81 (dd, ^2J = 11.5, J = 4.5 Hz, 2H), 3.29 (dd, ^2J = 11.5, J = 2.2 Hz, 1H), 3.23

(dd, ^{2}J = 11.5, J = 2.2 Hz, 1H), 3.11 (t, $J = {}^{4}J_{H\text{-}F}$ = 4.0 Hz, 1H), 2.17-2.03 (m, 1H), 1.85-1.75 (m, 1H), 1.74-1.64 (m, 1H), 1.46 (qd, $^{2}J = J$ = 12.1, J = 4.5 Hz, 1H), 1.36 (qd, $^{2}J = J$ = 12.1, J = 4.5 Hz, 1H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 138.6 (t, $^{2}J_{C\text{-}F}$ = 19.9 Hz), 117.0 (dd, $^{1}J_{C\text{-}F}$ = 262.8, 240.9 Hz), 114.1 (t, $^{3}J_{C\text{-}F}$ = 7.7 Hz), 94.1 (dd, $^{2}J_{C\text{-}F}$ = 26.1, 19.3 Hz), 83.0 (d, $^{3}J_{C\text{-}F}$ = 2.7 Hz), 68.6 (d, $^{3}J_{C\text{-}F}$ = 4.1 Hz), 67.7, 67.6, 34.0, 31.7, 29.0 ppm; ^{19}F NMR (376 MHz, DMSO-d_6): δ = -104.6 (d, ^{2}J = 236.8 Hz, 1F), -136.0 (d, ^{2}J = 236.8 Hz, 1F) ppm; (the ^{19}F-^{1}H splittings are not resolved in the 376 MHz ^{19}F NMR spectrum); $\bar{\nu}$/(neat) = 3287, 2846, 1446, 1297, 1052, 914 cm^{-1}; HRMS (APCI): calcd for $C_{11}H_{18}F_2O_3N_1$, 250.1249 $[M+NH_4]^+$, found: 250.1253;* MS (EI): *m/z* (%): 232 (2) $[M]^+$, 202 (7) $[M\text{-}C_2H_4]^+$,** t_R (GC) = 11.69 minutes.** *accurate mass was calculated for the ketone component. **the mixture appeared as one peak by GC-MS, masses corresponded to that of the ketone.

*4,4-Difluoro-5-methylene-2-phenyldihydro-2H-pyran-3(4H)-one (**7d**) and 3,3-dihydroxy-4,4-difluoro-5-methylene-2-phenyldihydro-2H-pyran (**8d**)*.

Ketone **7d** and hydrate **8d** were prepared according to general procedure D from propargyl ether **6d** (0.312 g, 1.00 mmol) with 1,3-*bis*(2,6-di*iso*propylphenyl-imidazol-2-ylidene)gold(I) chloride (5 mol %, 0.031 g) and silver hexafluoroantimonate(V) (5 mol %, 0.017 g) in 2-Methyltetrahydrofuran (6.0 mL). The crude material (0.324 g) was purified by flash column chromatography (40 g silica, 3 % acetone in dichloromethane) to afford an inseparable mixture of ketone **7d** and hydrate **8d** as a colourless solid (0.126 g, 52 %, 1:3.8). m.p. = 76-78 °C (recrystallised from ethyl acetate/hexane by vapour diffusion as a colourless plate); R_f = 0.53 (10 % acetone in dichloromethane); The following signals were attributed to both ketone **7d** and hydrate **8d** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64-7.32 (m, 5H) ppm; The following signals were attributed to ketone **7d** (assigned on the basis of δ and intensity); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.91-5.86 (m, 1H), 5.58 (app. q, $^{4}J_{H\text{-}F} = {}^{4}J$ = 1.5 Hz, 1H), 5.24

(t, $^4J_{H\text{-}F}$ = 3.1 Hz, 1H), 4.71 (app. dq, ^2J = 13.8, $^4J = {}^4J_{H\text{-}F}$ = 1.1 Hz, 1H), 4.61 (br. d, ^2J = 13.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.0 (dd, $^2J_{C\text{-}F}$ = 27.3, 23.4 Hz), 137.6 (t, $^2J_{C\text{-}F}$ = 19.3 Hz), 132.8, 128.6, 128.1, 127.0, 117.5 (t, $^3J_{C\text{-}F}$ = 7.4 Hz), 110.2 (dd, $^1J_{C\text{-}F}$ = 260.4, 248.7 Hz), 83.6, 67.8 (d, $^3J_{C\text{-}F}$ = 2.7 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -107.2 - -108.0 (m, including -107.6 (app. d, ^2J = 264.5 Hz, 1F)), -116.3 (d, ^2J = 264.5, 1F) ppm; (the ^{19}F-^{1}H splittings are not resolved in the 376 MHz ^{19}F NMR spectrum); The following signals were attributed to hydrate **8d** (assigned on the basis of δ and intensity); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.73 (d, $^4J_{H\text{-}F}$ = 4.9 Hz, 1H), 5.46 (app. q, $^4J_{H\text{-}F} = {}^4J$ = 1.7 Hz, 1H), 4.77-4.71 (m, 1H), 4.49 (dd, ^2J = 13.1, $^4J_{H\text{-}F}$ = 4.0 Hz, 1H), 4.38 (br. d, ^2J = 13.1 Hz, 1H), 2.88 (br. s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.1 (t, $^2J_{C\text{-}F}$ = 19.9 Hz), 133.0, 128.5, 127.9, 127.6, 115.5 (t, $^1J_{C\text{-}F}$ = 262.8 Hz), 115.2 (t, $^3J_{C\text{-}F}$ = 7.1 Hz), 92.2 (dd, $^2J_{C\text{-}F}$ = 27.7, 19.7 Hz), 80.5 (d, $^3J_{C\text{-}F}$ = 3.2 Hz), 68.7 (d, $^3J_{C\text{-}F}$ = 4.5 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -106.8 (d, ^2J = 242.3 Hz, 1F), -137.2 (app. dquint, ^2J = 242.3, $^4J_{F\text{-}H}$ = 2.0 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3306, 2905, 1713, 1326, 1203, 1047, 946 cm^{-1}; HRMS (APCI): calcd for $C_{12}H_{11}F_2O_2$, 225.0727 $[M+H]^+$, found: 225.0723;*MS (EI): *m/z* (%): 147 (4) $[M\text{-}C_6H_5]^+$, 90 (100) $[M\text{-}C_9H_9O]^+$,** t_R (GC) = 11.82 minutes.** *accurate mass was calculated for the ketone component of the mixture.**the mixture appeared as one peak by GC-MS, masses corresponded to that of the ketone.

*4,4-Difluoro-5-methylene-2-(4-(trifluoromethyl)phenyl)dihydro-2H-pyran-3(4H)-one (**7e**) and 3,3-dihydroxy-4,4-difluoro-5-methylene-2-(4-(trifluoromethyl)phenyl)dihydro-2H-pyran (**8e**)*. Ketone **7e** and hydrate **8e** were prepared according to general procedure D from propargyl ether **6e** (0.380 g, 1.00 mmol) with 1,3-*bis*(2,6-di*iso*propylphenyl-imidazol-2-ylidene)gold(I) chloride (5 mol %, 0.031 g) and silver hexafluoroantimonate(V) (5 mol %, 0.017 g) in 2-Methyltetrahydrofuran (6.0 mL). The crude material (0.376 g) was purified by flash column chromatography (40 g silica, 2 % acetone in dichloromethane) to afford an

inseparable mixture of ketone **7e** and hydrate **8e** as a colourless solid (0.161 g, 52 %, 1:6.1). R_f = 0.45 (5 % acetone in dichloromethane); The following signals were attributed to both ketone **7e** and hydrate **8e** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67, 7.65 (ABq, J_{AB} = 8.7 Hz, 4H) ppm; The following signals were attributed to ketone **7e** (assigned on the basis of δ and intensity); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, J = 8.4 Hz, 2H), 5.92-5.88 (m, 1H), 5.61 (q, $^4J_{H\text{-}F} = {}^4J$ = 1.4 Hz, 1H), 5.30 (t, $^4J_{H\text{-}F}$ = 3.2 Hz, 1H), 4.73 (dq, ^2J = 13.9, $^4J = {}^4J_{H\text{-}F}$ = 1.2 Hz, 1H), 4.64 (br. d, ^2J = 13.9 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.2 (dd, $^2J_{C\text{-}F}$ = 27.7, 23.4 Hz), 137.3 (t, $^2J_{C\text{-}F}$ = 19.1 Hz), 136.5, 130.7 (q, $^2J_{C\text{-}F}$ = 32.8 Hz), 127.2, 125.0 (q, $^3J_{C\text{-}F}$ = 3.9 Hz), 117.9 (t, $^3J_{C\text{-}F}$ = 7.5 Hz), 110.2 (dd, $^1J_{C\text{-}F}$ = 260.3, 247.3 Hz), 82.7, 68.1 (d, $^3J_{C\text{-}F}$ = 3.3 Hz) ppm (the large ^1J CF_3 quartet could not be observed in the 100 MHz ^{13}C NMR spectrum); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.8 (s, 3F), -107.0 (d, ^2J = 265.4 Hz, 1F), -117.4 (d, ^2J = 265.4, 1F) ppm (the ^{19}F-^{1}H splittings are not resolved in the 376 MHz ^{19}F NMR spectrum); The following signals were attributed to hydrate **8e** (assigned on the basis of δ and intensity); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.76 (d, $^4J_{H\text{-}F}$ = 4.8 Hz, 1H), 5.49 (app. q, $^4J_{H\text{-}F} = {}^4J$ = 1.8 Hz, 1H), 4.82-4.77 (m, 1H), 4.51 (dd, ^2J = 13.1, $^4J_{H\text{-}F}$ = 4.1 Hz, 1H), 4.38 (br. d, ^2J = 13.1 Hz, 1H), 3.09 (br. s, 1H), 2.81 (br. s, 1H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.2, 135.7 (t, $^2J_{C\text{-}F}$ = 20.2 Hz), 130.5 (q, $^2J_{C\text{-}F}$ = 32.6 Hz), 128.1, 124.5 (q, $^3J_{C\text{-}F}$ = 3.7 Hz), 123.8 (q, $^1J_{C\text{-}F}$ = 272.3 Hz), 115.6 (t, $^3J_{C\text{-}F}$ = 7.1 Hz), 115.3 (dd, $^1J_{C\text{-}F}$ = 261.8, 242.8 Hz), 92.3 (dd, $^2J_{C\text{-}F}$ = 28.6, 20.8 Hz), 79.9 (d, $^3J_{C\text{-}F}$ = 2.8 Hz), 68.7 (d, $^3J_{C\text{-}F}$ = 4.6 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.7 (s, 3F), -106.9 (d, ^2J = 241.7 Hz, 1F), -137.2 (app. dquint, ^2J = 241.7, $^4J_{F\text{-}H}$ = 1.9 Hz, 1F) ppm; $\bar{\nu}$/(neat) = 3621, 3259, 2921, 1708, 1323, 1067, 952 cm^{-1}; HRMS (APCI): calcd for $C_{13}H_{13}F_5O_2N_1$, 310.0861 $[M+NH_4]^+$, found: 310.0857;* MS (EI): *m/z* (%): 292 (1) $[M]^+$, 145 (63) $[C_7H_4F_3]^+$, 90 (100) $[M\text{-}C_{10}H_8F_3O]^+$,** t_R (GC) = 11.57 minutes.** *accurate mass was calculated for the ketone

component of the mixture.**the mixture appeared as one peak by GC-MS, masses corresponded to that of the ketone.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Copies of spectroscopic data (^{1}H, ^{13}C and ^{19}F) for all products and X-ray crystallographic data.

Acknowledgements

We thank the Carnegie Trust for a Carnegie-Caledonian PhD scholarship and Dr Vipulkumar Patel (GSK Flexible Discovery Unit) for additional support, the EPSRC National Mass Spectrometry Service Centre, Swansea for accurate mass measurements, Dr Alan R Kennedy for crystal structures and the EPSRC UK National Crystallography Service, Southampton for data collection on compound **8c** and Craig Irving (NMR Technician, University of Strathclyde) for assistance with NMR experiments.

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