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Multicomponent reactions of methyl substituted all-*cis* tetrafluorocyclohexane aldehydes†

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This paper reports the preparation of methyl substituted all-*cis* tetrafluorocyclohexanes prepared from a Birch reduction of benzoic acid, worked up with a methyl iodide quench. The resultant methyl-cyclohexadiene carboxylic acid was reduced to the alcohol, protected as an ether and then a sequence of functional group manipulations carried out to introduce four fluorines. The cyclohexadienyl ring was then epoxidised and the C–O bonds sequentially converted through deoxyfluorination reactions to two sets of isomers of all-*cis* tetrafluorocyclohexane isomers. The blocking methyl group renders the ring safe to hydrogen fluoride elimination. Deprotection of the benzylic ether and then oxidation gave aldehydes which were then used in Ugi and Passerini multicomponent reactions, allowing this facially polarised cyclohexane to be incorporated into peptidic structural motifs.

1. Introduction

We have recently described the synthesis and properties of the all-*cis* 2,3,5,6-tetrafluorocyclohexane **1** ring system.[1] The stereochemistry is such that in the chair conformation the four fluorine atoms are all on one face of the cyclohexane ring. Also two of the C–F bonds are 1,3-diaxial and align parallel to each other and this results in an orientated polarity, which is supplemented by the two equatorial C–F bonds which are also on the upper face of the cyclohexane ring (Fig. 1). The outcome is a large molecular dipole moment of 5.2 Dy for **1**.[1] The motif is polar hydrophobic and an interesting and unusual aspect of the cyclohexane ring system is that it has facial polarity, therefore it becomes attractive to access building blocks which might be used to introduce the motif into drug discovery and

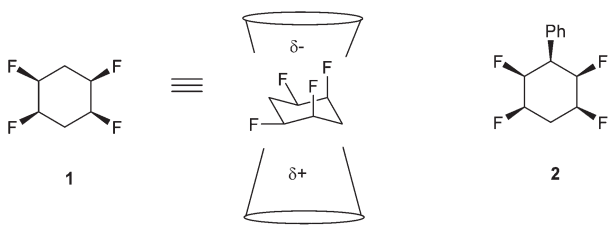

Fig. 1 All-*cis*-tetrafluorocyclohexane **1** is facially polarised (μ = 5.2 D), with a more negative fluorine face and a more positive hydrogen face.[1]

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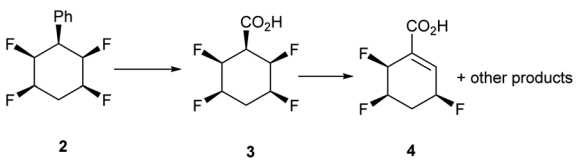
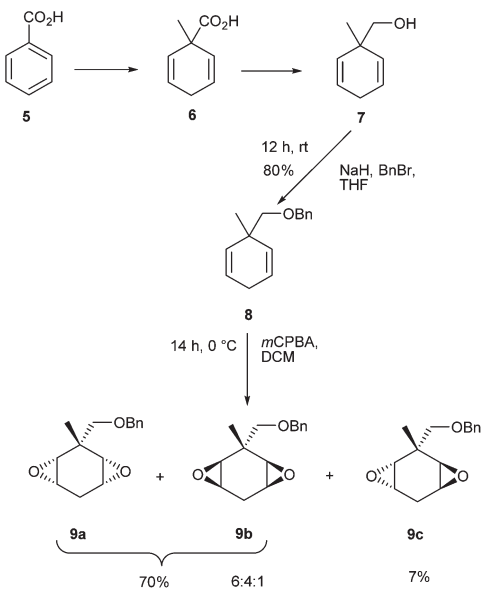
† Electronic supplementary information (ESI) available. CCDC 1436752–1436761. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ob02334c



Scheme 1 Carboxylic acid **3** is unstable to dehydrofluorination.



Scheme 2 Synthesis of diepoxides **9a, b, c** from benzoic acid **5**.

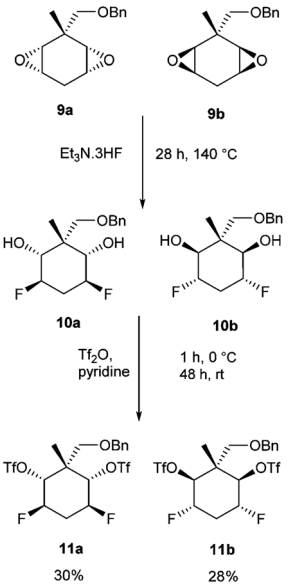
agrochemical research programmes. Derivatives of the ring system are relatively challenging to prepare, however recently we reported the preparation of phenyl derivative **2** and then access to a variety of aryl derivatives by standard electrophilic aromatic substitution reactions of **2**.[2–4]

In order to build further structural diversity around this motif, cyclohexane carboxaldehyde derivatives are reported, carrying a methyl group alpha to the carbonyl group. The methyl group is a design feature placed to protect against hydrogen fluoride elimination. The utility of the aldehydes in multicomponent reactions has allowed a library of peptidic analogues to be prepared.[5,6]

2. Results and discussion

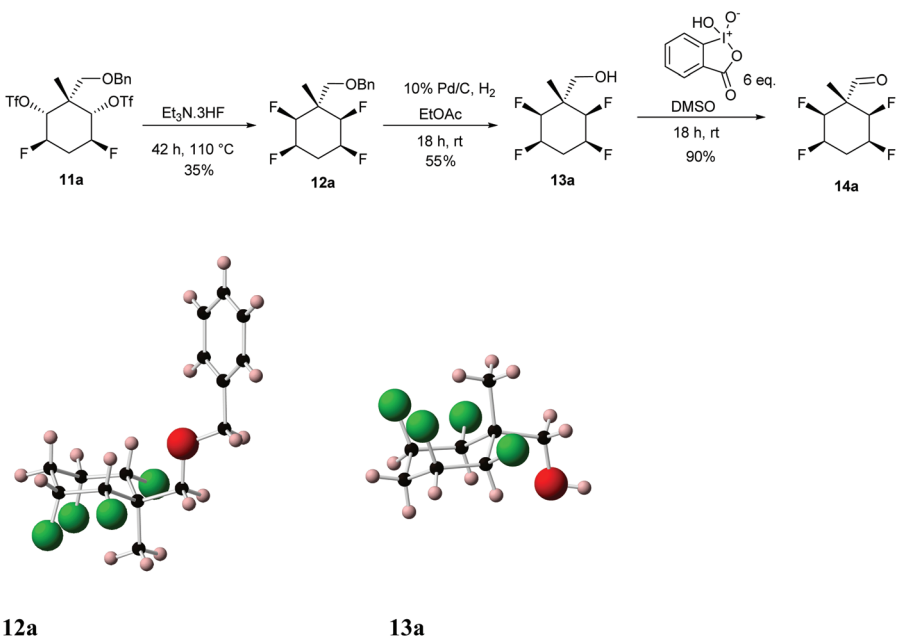
At the outset a direct oxidation of phenyl derivative **2** was explored. The corresponding carboxylic acid **3** was the anticipated product, however it proved difficult to characterize in our hands as it is very vulnerable to hydrogen fluoride elimination to products related to **4**, due to the relatively acidic hydrogen atom, alpha to the carboxylic acid derivative (Scheme 1).

In order to circumvent this problem it became an objective to replace the alpha hydrogen with a methyl group and generate a more stable motif. Following a literature procedure, the Birch reduction of benzoic acid **5** followed by *in situ* methylation afforded α-methylated carboxylic diene **6**, which was then reduced with $LiAlH_4$ to give alcohol **7** in good yield.[7] Protection of the primary alcohol **7** with benzyl bromide furnished ether **8** (80% yield), which was then epoxidised using an excess of *m*CPBA.[8,9] Three diastereoisomers of the diepoxide were generated, *cis* (**9a** and **9b**) and *trans* (**9c**) in 6 : 4 : 1 ratio (Scheme 2).



Scheme 3 Ring opening fluorination of diepoxides **9a** and **9b** and then activation to ditriflates **11a** and **11b**.

The *trans*-diepoxide stereoisomer **9c** was separated (7%) from the inseparable *cis*-diepoxides **9a** and **9b** (70%). The configuration of the epoxides was determined by ^{1}H NMR spectroscopy. The *cis*-diepoxides (**9a** and **9b**) could be differentiated from the *trans* through the methylene hydrogen atoms H-4a and H-4b. For the *trans*-diastereoisomer, both hydrogens are in similar environments and appear as unresolved signals (δ 2.30 ppm), whereas for the *cis*-diepoxides (**9a** and **9b**), these hydrogens are non-equivalent and resolve into a pair of multiplets (δ 2.77 ppm and δ 2.24 ppm).



Scheme 4 Preparation of aldehyde **14a** from di-triflate **11a** and showing the X-ray structures of **12a** and **13a**.

Treatment of the diepoxide mixture **9a** and **9b** with $Et_3N{\cdot}3HF$ at 140 °C, resulted in their full conversion to difluoro diols **10a** and **10b** as determined by NMR (Scheme 3). This mixture was then reacted with triflic anhydride which resulted in the diastereoisomeric triflates **11a** and **11b**. These products could be separated by chromatography and were recovered in yields of 30% (**11a**) and 28% (**11b**) respectively (Scheme 3).

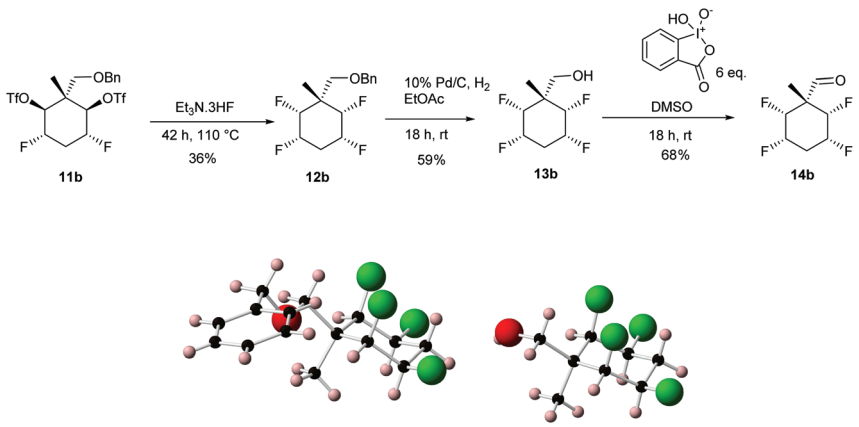
Diastereoisomer **11a** was treated with $Et_3N{\cdot}3HF$ at 110 °C for a prolonged period which generated tetrafluorocyclohexane **12a**. *O*-Debenzylation (10% Pd/C/H_2) generated alcohol **13a** as illustrated in Scheme 4.[10]

The structures and stereochemistry of products **12a** and **13a** were confirmed by X-ray crystallography and are shown in Scheme 4. An analogous procedure was carried out on diastereoisomer **11b**, to generate aldehyde diastereoisomer **14b**. Again the X-ray structures of benzyl ether **12b** and deprotected alcohol **13b** were obtained to confirm stereochemistry and they are shown in Scheme 5. Finally oxidation of alcohols **13a** and **13b** using IBX in DMSO, gave aldehydes **14a** (90%) and **14b** (68%) respectively.[11,12]

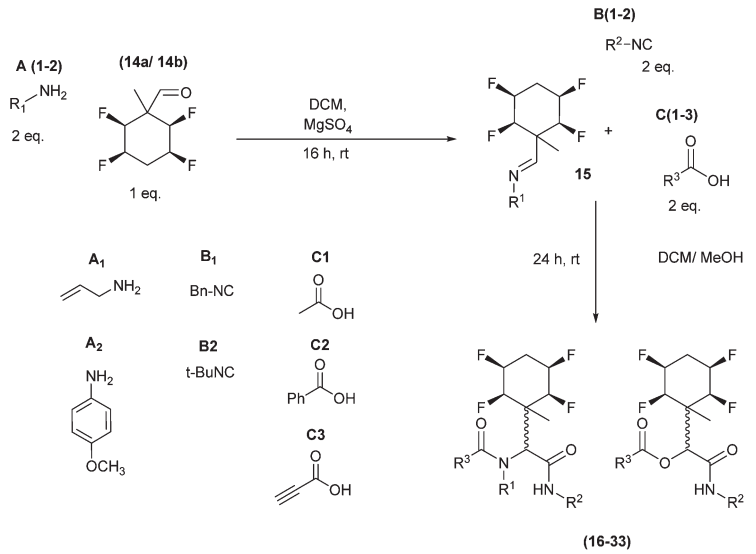
The application of aldehydes **14a** and **14b** in Ugi four-component reactions was explored.[5,6,13] In the first instance imines **15** were formed from the condensation of tetrafluoro aldehydes **14a**/**14b** with a candidate amines A1/A2, and then individual isocyanides **B** and carboxylic acids **C** were added as illustrated in Scheme 6.

A series of reactions were conducted to generate a small chemical library of peptidomimetics **16–32** carrying the tetrafluorocyclohexyl ring motif. These compounds are all racemic as a new stereogenic centre is generated.

While some products were obtained by classic four component Ugi reactions, others derive from the Passerini reaction (Tables 1 and 2), through direct reaction of the free aldehyde **14** rather than the preformed imine **15**, with the added isocyanides **B** and carboxylic acids C.[13–17] In most cases the four component reactions were found to produce both, the



Scheme 5 Preparation of aldehyde **14b** from ditriflate **11b** and showing the X-ray structures of **12b** and **13b**.



Scheme 6 General Ugi procedure involving aldehydes **14a** and **14b** and a range of amines (**A1–2**), isocyanides (**B1–2**) and carboxylic acids (**C1–3**).

Table 1 Compounds produced using aldehyde **10a** in U-4CC reactions

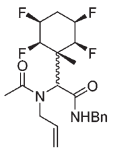
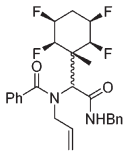
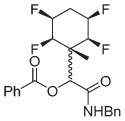
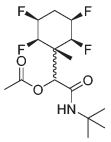
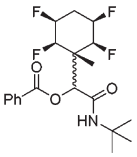
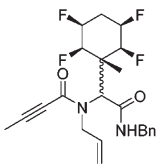
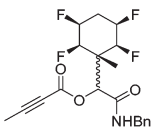
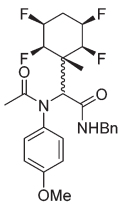
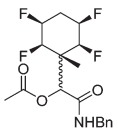
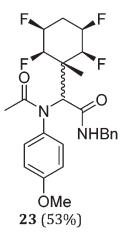
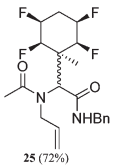
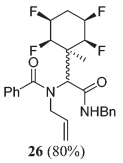
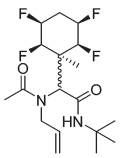
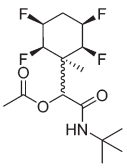
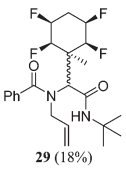
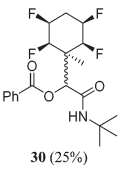
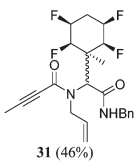
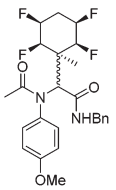
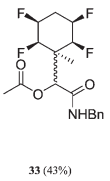
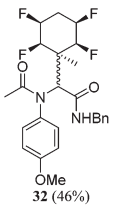
Entry	R^1CNH_2	R^2CN	R^3COOH	Conditions (time, temp, solvent)	Ugi (yield)	Passerini (yield)	Ratio (1 : 2)
1	**A1**	**B1**	**C1**	40 h, 30 °C, DCM	 **16** (58%)	N/A	—
2	**A1**	**B1**	**C2**	40 h, 25 °C, DCM	 **17** (25%)	 **18** (20%)	2 : 1
3	**A1**	**B2**	**C1**	40 h, 25 °C, DCM	N/A	 **19** (82%)	—
4	**A1**	**B2**	**C2**	40 h, 25 °C, DCM	N/A	 **20** (79%)	—
5	**A1**	**B1**	**C3**	40 h, 25 °C, DCM	 **21** (22%)	 **22** (30%)	1 : 2.5
6	**A2**	**B1**	**C1**	40 h, 25 °C, DCM	 **23** (25%)	 **24** (37%)	4 : 5
7	**A2**	**B1**	**C1**	40 h, 25 °C, MeOH	 **23** (53%)	N/A	

Table 2 Compounds produced using aldehyde **10b** in U-4CC reactions

Entry	R^1CNH_2	R^2CN	R^3COOH	Conditions (time, temp, solvent)	Product **1** (yield)	By-product (yield)	Ratio (1: 2)
8	**A1**	**B1**	**C1**	40 h, 30 °C, DCM	 **25** (72%)	N/A	—
9	**A1**	**B1**	**C2**	40 h, 25 °C, DCM	 **26** (80%)	N/A	—
10	**A1**	**B2**	**C1**	40 h, 25 °C, DCM	 **27** (26%)	 **28** (41%)	1 : 2
11	**A1**	**B2**	**C2**	40 h, 25 °C, DCM	 **29** (18%)	 **30** (25%)	1 : 2
12	**A1**	**B1**	**C3**	40 h, 25 °C, DCM	 **31** (46%)	N/A	—
13	**A2**	**B1**	**C1**	40 h, 25 °C, DCM	 **32**	 **33** (43%)	1 : 8
14	**A2**	**B1**	**C1**	40 h, 25 °C, MeOH	 **32** (46%)	N/A	—

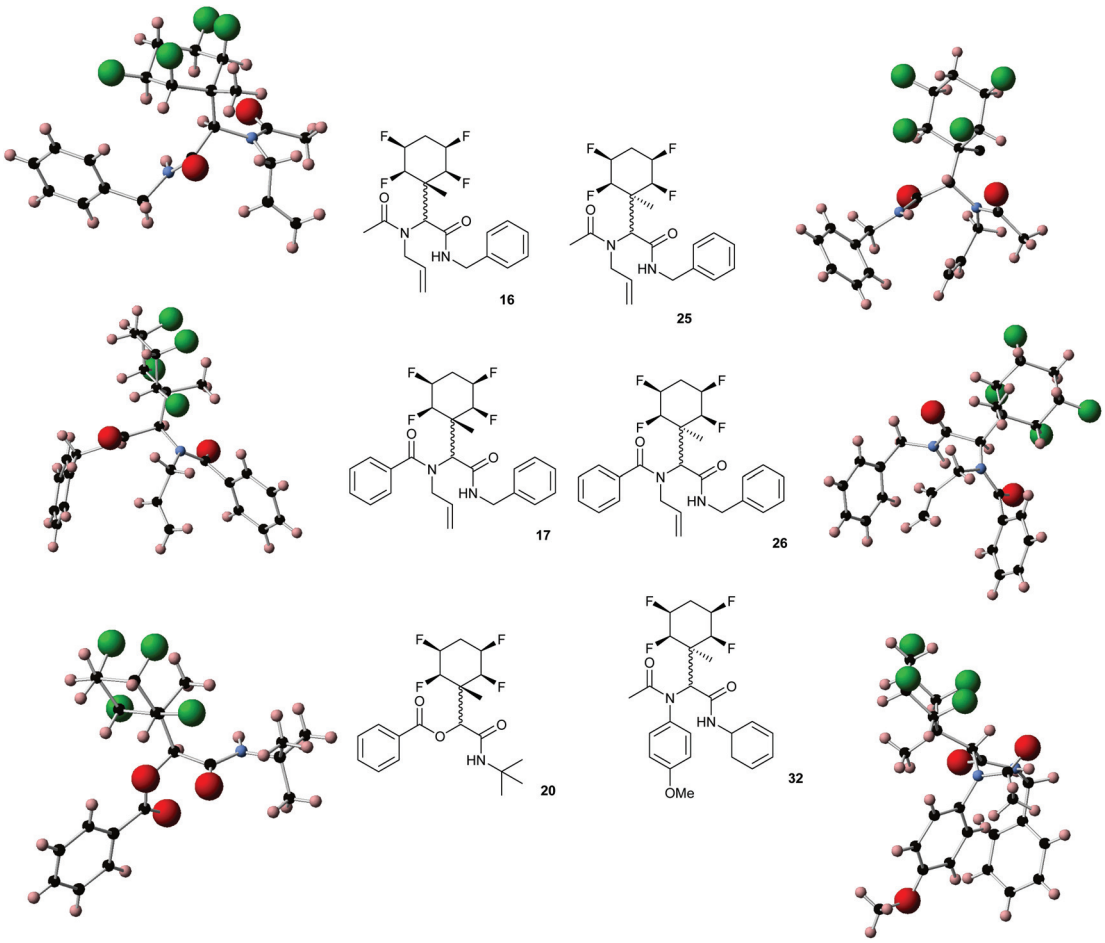


Fig. 2 X-ray structures of a selected α-aminoacyl amides **16**, **17**, **25**, **26**, **32** which derive from reaction entries 1,2,8,9 and 14 in Table 1, and of the Passerini by-product **20** from reaction entry 3 of Table 1.

α-aminoacyl amide Ugi derivatives and α-hydroxy carboxamide Passerini type products. The crystal structures of several Ugi products **16–17**, **25–26**, **32** and a Passerini α-acyloxy amide **20** are shown of Fig. 2. In each case compensating enantiomers of these racemic products are obvious in the unit cell of each crystal structure. The $^{19}F\{^1H\}$-NMR spectra of these compounds merit some comment. For example the $^{19}F\{^1H\}$-NMR spectra of aldehydes **4a** and **4b** have two sets of equivalent fluorines, which show clear AA′XX′ second order spectra, however for the multicomponent products a stereogenic centre is generated and the two sets of originally equivalent fluorines become diastereotopic and all four become chemically non-equivalent and they resolve to varying extents.

3. Conclusion

In summary we report the synthesis of aldehyde diastereoisomers **14a** and **14b**, containing the all-*syn* 1,2,4,5-tetrafluorocyclohexane motif. These aldehydes are rendered stable to dehydrofluorination by having a blocking alpha methyl group. Aldehydes **14a** and **14b** were used as key components for Ugi four component reactions and in the event both α-aminoacyl amide and α-hydroxy carboxamide derivatives were generated. This approach allows the facially polarized all-*cis* tetrafluorocyclohexane motif to be introduced into peptidomimetic scaffolds for exploration in bioactivity screening programmes.

Acknowledgements

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