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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.

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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 ($\mu = 5.2 \text{ D}$), with a more negative fluorine face and a more positive hydrogen face.¹



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Scheme 1 Carboxylic acid 3 is unstable to dehydrofluorination.



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

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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 LiAlH₄ 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 ¹H 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.

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Treatment of the diepoxide mixture **9a** and **9b** with Et₃N·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/H₂) 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).

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

Entry	R ¹ CNH ₂	R ² CN	R ³ COOH	Conditions (time, temp, solvent)	Ugi (yield)	Passerini (yield)	Ratio (1:2)
1	A1	B1	C1	40 h, 30 °C, DCM	F F N NHBn 16 (58%)	N/A	_
2	A1	B1	C2	40 h, 25 °C, DCM	F F Ph N N HBn 17 (25%)	F F Ph H H H H H H H H H H H H H H H H H H	2:1
3	A1	B2	C1	40 h, 25 °C, DCM	N/A	F F O HN 19 (82%)	_
4	A1	B2	C2	40 h, 25 °C, DCM	N/A	F F Ph O HN 20 (79%)	_
5	A1	B1	C3	40 h, 25 °C, DCM	F F N N NHBn 21 (22%)	F F F NHBn 22 (30%)	1:2.5
6	A2	B1	C1	40 h, 25 °C, DCM	F F F N NHBn 23 (25%)	F F F F F F F F F F	4:5
7	A2	B1	C1	40 h, 25 °C, MeOH	F F N NHBn	N/A	

 OMe 23 (53%)

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

Entry	R ¹ CNH ₂	R ² CN	R ³ COOH	Conditions (time, temp, solvent)	Product 1 (yield)	By-product (yield)	Ratio (1: 2)
3	A1	B1	C1	40 h, 30 °C, DCM	F F NHBn 25 (72%)	N/A	_
9	A1	B1	C2	40 h, 25 °C, DCM	F F Ph N N N N N N N N HBn 26 (80%)	N/A	_
10	A1	B2	C1	40 h, 25 °C, DCM	F F HN 27 (26%)	F F F O HN 28 (41%)	1:2
11	A1	B2	C2	40 h, 25 °C, DCM	F F F Ph N HN E 29 (18%)	F F Ph 0 HN 30 (25%)	1:2
12	A1	B1	C3	40 h, 25 °C, DCM	F F N NHBn 31 (46%)	N/A	-
13	A2	B1	C1	40 h, 25 °C, DCM	F F F N N HBn OMe 32	F F F F F F F F F F F F F F F F F F F	1:8
14	A2	B1	C1	40 h, 25 °C, MeOH	F F H NHBn 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 ¹⁹F{¹H}-NMR spectra of these compounds merit some comment. For example the ¹⁹F{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 nonequivalent 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.

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References

 A. J. Durie, A. M. Z. Slawin, T. Lebl, P. Kirsch and D. O'Hagan, *Chem. Commun.*, 2012, 48, 9643–9645, DOI: 10.1039/C2CC34679F.

- 2 M. S. Ayoup, D. B. Cordes, A. M. Z. Slawin and D. O'Hagan, Org. Biol. Chem., 2015, 13, 5621–5624, DOI: 10.1039/ C5OB00650C.
- 3 A. J. Durie, T. Fujiwara, R. Cormanich, M. Bühl, A. M. Z. Slawin and D. O'Hagan, *Chem. – Eur. J.*, 2014, **20**, 6259–6263, DOI: 10.1002/chem.201400354.
- 4 A. J. Durie, T. Fujiwara, N. Al-Maharik, A. M. Z. Slawin and D. O'Hagan, *J. Org. Chem.*, 2014, **79**, 8228–8233, DOI: 10.1021/jo501432x.
- 5 I. Ugi, A. Demharter, W. Hörl and T. Schmid, *Tetrahedron*, 1996, **52**, 11657–11664, DOI: 10.1016/0040-4020(96)00647-3.
- 6 I. Ugi, B. Werner and A. Dömling, *Molecules*, 2003, **8**, 53–66, DOI: 10.3390/80100053.
- 7 I. Usui, K. Nomura and B. Breit, Org. Lett., 2011, 13, 612–615, DOI: 10.1021/ol1028546.
- 8 N. N. Schwartz and J. H. Blumbergs, *J. Org. Chem.*, 1964, **29**, 1976–1979, DOI: 10.1021/j001030a078.

- 9 H. Huang, C. G. Nelson and D. F. Taber, *Tetrahedron Lett.*, 2010, 51, 3545–3546, DOI: 10.1016/j.tetlet.2010.04. 129.
- 10 D. C. Johnson and T. S. Widlanski, Org. Lett., 2004, 6, 4643-4646, DOI: 10.1021/ol048426w.
- 11 M. Frigerio, M. Santagostino and S. Sputore, *J. Org. Chem.*, 1999, **64**, 4537–4538, DOI: 10.1021/jo9824596.
- 12 S. D. Meyer and S. L. Schreiber, *J. Org. Chem.*, 1994, **59**, 7549–7552, DOI: 10.1021/j000103a067.
- 13 A. Dömling, Chem. Rev., 2006, 106, 17–89, DOI: 10.1021/ cr0505728.
- 14 M. Passerini and L. Simone, *Gazz. Chim. Ital.*, 1921, **51**, 126–129.
- 15 M. Passerini and G. Ragni, Gazz. Chim. Ital., 1931, 61, 964–969.
- 16 L. Banfi and R. Riva, *Org. React.*, 2005, **65**, 1–140, DOI: 10.1002/0471264180.or065.01.
- 17 L. Weber, K. Illgen and M. Almstetter, Synlett, 1999, 366–374, DOI: 10.1055/s-1999-2612.