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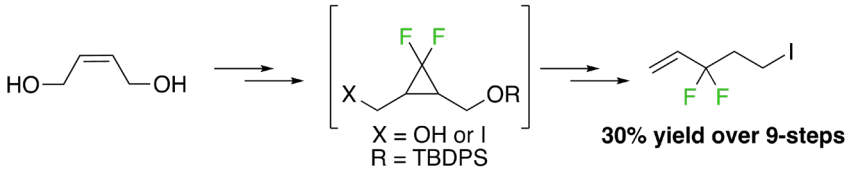

# Synthesis of an allylic *gem*-difluoromethylene building block *via* radical-mediated difluorocyclopropane ring opening

Kirsty Milne, Martyn C. Henry and Craig Jamieson*

*Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow, G1 1XL United Kingdom*

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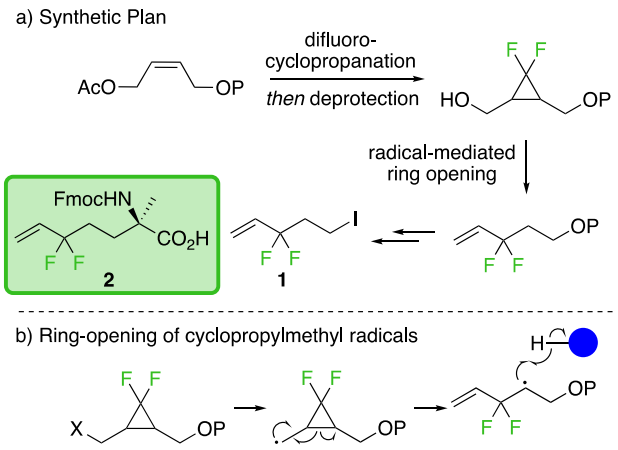
ABSTRACT

We report an optimised and highly efficient synthetic route towards a valuable functionalised fluorinated building block. The key-steps include difluorocyclopropanation of a disubstituted alkene with a suitable difluorocarbene precursor, and a radical-induced cyclopropane ring-opening, operating *via* an iodide atom transfer reaction.

## 1. Introduction

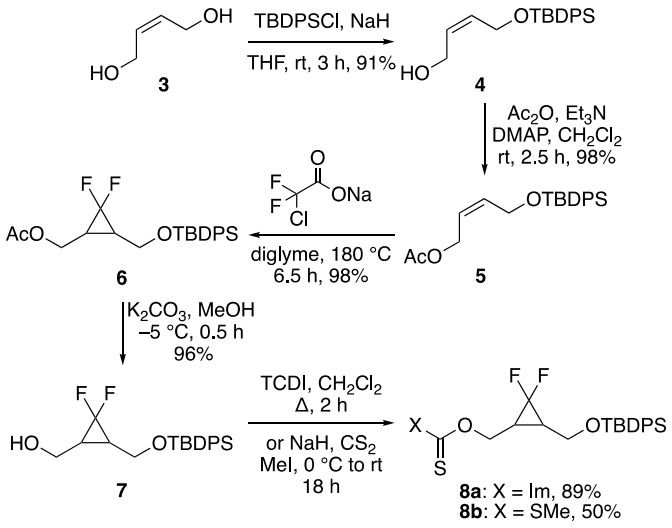
The incorporation of fluorine into organic compounds has the potential to considerably alter the physical, chemical and biological properties of a molecule and hence has widespread application in medicinal chemistry,[1] agrochemistry[2] and materials science.[3] Within the drug discovery tool kit, the substitution of a methylene unit for a *gem*-difluoromethylene system can impart substantial structural and electronic modifications upon a molecule which can have significant ramifications, particularly with regards to a compound's binding affinity and biological activity.[1(c)] The large electron-withdrawing effect of the fluorine atoms can have an important effect on the pKa of adjacent protons while the increase in internal angle can also influence ground-state conformations.[4] The $CH_2$ to $CF_2$ substitution is especially useful as a means to modulate physicochemical parameters such as lipophilicity and polar surface area and can offer an improvement of the metabolic stability of certain drug molecules.[5] Furthermore, the $CF_2$ fragment has been extensively used as an oxygen bioisostere in heteroaryl ethers, phosphonates, sulfonic acids, sulfonamides and various heterocycles.[6] The importance of the *gem*-difluoroalkyl group has resulted in the development of a vast array of synthetic methods to selectively install this functionality.[7,8] Traditionally, deoxyfluorination of aldehydes and ketones using diethylaminosulfur trifluoride (DAST), Ishikawa's reagent and a range of other nucleophilic fluorinating reagents has been the mainstay of synthetic methods to access this motif.[9] However, this difluorination approach requires expensive fluorinating reagents and relies on harsh conditions such as strong acids and oxidants which can result in significant functional group incompatibilities. It is for this reason that alternative approaches towards the synthesis of *gem*-difluoromethylene compounds have been developed which involve the use of appropriate building blocks featuring a pre-installed *gem*-difluoromethyl functional group.[10] Included among these protocols is difluorocyclopropanation with a suitable difluorocarbene precursor and subsequent ring opening which represents an attractive and economical route towards *gem*-difluoromethyl compounds.[11,12] We were interested in developing a tractable and scalable synthesis of *gem*-difluoromethyl building block **1** that could potentially be used in the preparation of bespoke $S_5$ amino acid **2**, a precursor to a novel fluorine containing stapled peptide (Scheme 1a). Stapled peptides are emerging therapeutic tools, designed to mimic protein secondary structures, namely the α-helix, with the aim of targeting and mediating specific protein-protein interactions.[13] The inclusion of fluorine atoms to the linker of stapled peptides has the potential to tune the helicity of the system resulting in enhancement of potency, cell permeability and helical stability. The basis of our strategy for the synthesis of building block **1** involves the introduction of the *gem*-difluoro functionality *via* the cyclopropanation of an alkene in the presence of an appropriate source of the highly reactive fluorinated carbene. This would then allow us to exploit the well known propensity of cyclopropylmethyl radicals to undergo β-C–C bond scission to give 3-butenyl radicals,[14] which can then be intercepted with a suitable H-donor (Scheme 1b). Deprotection and subsequent functional group interconversion would then afford the desired functionalised *gem*-difluorinated building block **1**.




**Scheme 1: Synthetic approach to fluorinated building block 1**

## 2. Results and Discussion

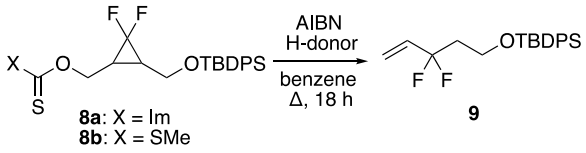
The first stage in our synthesis involved the orthogonal protection of (*Z*)-butene-1,4-diol (**3**) to give a suitable alkene precursor for the difluorocyclopropanation reaction (Scheme 2). Mono-protection of **3** using TBDPS chloride and sodium hydride gave the corresponding TBDPS silyl ether **4** in 91% yield. This was followed by the acetylation of **4** using acetic anhydride and triethyl amine in the presence of DMAP, which gave doubly protected diol **5** in 98% yield. The subsequent part of the synthesis required the construction of difluorocyclopropane ring from alkene **5**. Accordingly, difluorocarbene was generated *in situ* by the thermal decomposition of sodium chlorodifluoroacetate (NaCDFA),[15] and was reacted with alkene **5** at 180 °C. Analysis of the crude reaction mixture by $^{1}$H NMR spectroscopy revealed a 2:1 mixture of cyclopropane **6** and alkene **5**, which were inseparable by flash column chromatography. Fortunately, slow addition of NaCDFA over the course of five hours, followed by an additional 1.5 h at 180 °C, resulted in full conversion to *gem*-difluorocyclopropane **6**, which was then isolated in 98% yield.[16] Acetate deprotection under basic conditions at −5 °C resulted in the formation of alcohol **7** in 96% yield, without removal of the silyl ether. Xanthates **8a** and **8b**, for use in the Barton-McCombie deoxygenation,[12(b)] were prepared by reaction of alcohol **7** with thiocarbonyldiimidazole (TDCI) and carbon disulfide followed by methylation with methyl iodide, respectively.




**Scheme 2: Difluorocyclopropanation and xanthate synthesis**

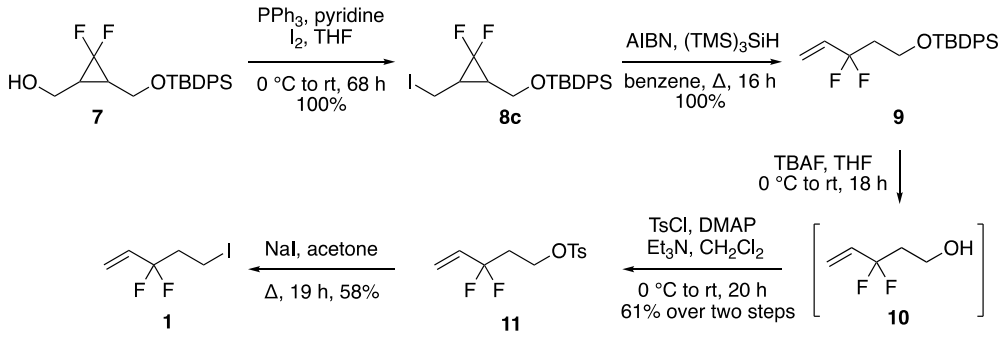
With xanthates **8a** and **8b** in hand, these were next subjected to the key Barton-McCombie deoxygenation reaction (Table 1). Reaction of thiocarbamate **8a** with tributyltin hydride initiated with AIBN resulted in only 17% conversion of starting material **8a** to ring opened product **9** (entry 1). The use of xanthate **8b** under the same conditions resulted in a marginal improvement of the observed conversion to **9** (entry 2). In order to improve the conversion, the H-donor was exchanged from $Bu_3SnH$ to tris(trimethylsilyl)silane ($(TMS)_3SiH$).[17] As well as negating the use of toxic tin reagents, there is a significant thermodynamic rationale for the substitution of $Bu_3SnH$ with $(TMS)_3SiH$. While the bond dissociation of the Si–H bond is proximate to that of the Sn–H bond, the resultant Si–S bond (617 kJ/mol)[18] is significantly stronger than the corresponding Sn–S bond (467 kJ/mol)[18] providing a much stronger driving force for the deoxygenation reaction. Reaction of imidazole xanthate **8a** with $(TMS)_3SiH$ under the previously examined conditions resulted in a 71% conversion to desired ring opened product **9** (entry 3). The use of xanthate **8b** did not improve the reaction outcome and reduced the conversion of **8b** to **9** to 60% (entry 4).

**Table 1: Radical-mediated cyclopropane ring opening optimization, a) Determined using $^{19}$F NMR spectroscopy**




| Entry | X | H-donor | Conversion (%)[a] |
|---|---|---|---|
| 1 | Im | $Bu_3SnH$ | 17 |
| 2 | SMe | $Bu_3SnH$ | 38 |
| 3 | Im | $(TMS)_3SiH$ | 71 |
| 4 | SMe | $(TMS)_3SiH$ | 60 |

Guided by the work of Kobayashi and co-workers, it was reasoned that an iodine transfer reaction could prove more effective in the generation of the requisite cyclopropylmethyl radical, and hence result in a more efficient ring-opening transformation.[12(b)] To achieve this, an Appel reaction with triphenylphosphine and iodine in the presence of pyridine was used to convert alcohol intermediate **7** to alkyl iodide **8c** in quantitative yield (Scheme 3).




**Scheme 3: Radical-mediated ring opening and completion of synthesis**

Iodide **8c** was then submitted to the radical-mediated ring-opening using AIBN as the initiator and $(TMS)_3SiH$ as the hydrogen atom source which gave *gem*-difluoroalkene **9** in an excellent yield. In addition to quantitative yield observed with the use of $(TMS)_3SiH$, crucially this also avoided the toxicity and environmental concerns associated with the use of $Bu_3SnH$.

The next stage of the synthesis involved the removal of the TBDPS protecting group. While initial attempts to cleave the silyl ether in methanolic hydrochloric acid solution resulted in full conversion of the starting material, attempts to isolate alcohol intermediate **10** were unsuccessful due to its volatility and thermal instability. Based on this, resin supported TBAF was used to aid in the isolation of **10** however, no conversion from **9** was observed under these conditions. An alternative strategy was proposed that involved deprotection of silyl ether **9** followed by direct conversion of the crude alcohol **10** to the corresponding tosylate **11**, precluding isolation of **10** and hence circumventing the associated stability issues.[19] TBAF-mediated removal of the TBDPS protecting group resulted in the formation of alcohol **10** which was then subjected to tosylation under standard conditions. This allowed the isolation of sulfonate **11** in 61% yield over the two steps. To complete the synthesis, tosylate **11** was subjected to a Finkelstein-type substitution reaction using sodium iodide which gave the target fluorinated building block **1** in 58% yield.[20]

In summary, we have developed a highly efficient synthesis of fluorinated building block **1** in 30% yield over 9-steps from (*Z*)-butene-1,4-diol (**3**). The geminal difluoromethylene motif was introduced *via* an alkene difluorocyclopropantion with NaCDFA as the $CF_2$ carbene source, without the requirement of expensive fluorinating reagents. Our strategy then exploited the highly strained nature of the *gem*-difluorocyclopropane moiety in a radical-induced tandem dehalogenation/ring opening sequence. Subsequently, the stability and volatility issues related with pentenyl alcohol intermediate **10** were avoided by using a two-step deprotection/tosylation strategy which then allowed facile access to target building block **1** by substitution with sodium iodide. Current efforts in our laboratory are focusing on the application of the *gem*-difluorinated building block **1** in the enantioselective synthesis of a fluorinated $S_5$ amino acid analogue **2**, as well as exploring structure-property relationships upon incorporation into a palette of stapled peptides.

## Acknowledgments

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## Appendix A: Supplementary Material

Experimental procedures and spectral data for all compounds are included

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20. Compound **1** was isolated with 90% purity, with a 10% impurity of *n*-pentane, due its inherent volatility.