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Fluorination Homologation of Biorenewable Synthon Cyrene

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Abstract: A one-carbon difluorocyclopropanation/ring-expansion has been developed for the chiral synthon Cyrene, which is obtained via cellulose pyrolysis. The ring-enlargement was achieved by converting Cyrene (dihydrolevoglucosenone) into an enamine, reacting it with an in situ-generated difluorocarbene, and then heating it to ring-open the cyclopropane. Access to the product provides access to fluorinated analogues of this valuable chiral biomass derivative.

Keywords: ring expansion; difluorocyclopropane; green chemistry; levoglucosenone; cyrene

1. Introduction

The biomass derivatives levoglucosenone (**1**) and its commercially available reduced form Cyrene (**2**), which are obtained from the acid-catalysed pyrolysis of cellulose, have emerged as promising chiral platform chemicals in materials chemistry (Figure 1) [1,2] and building blocks for the production of pharmaceuticals or natural products [3–7]. Transformations developed for **1** and **2** have provided routes to a variety of C_6 synthons after 1,6-anhydro bridge-opening [8,9] and C_5 synthons following Baeyer–Villiger oxidation [10,11]. Access to C_7 chiral synthons would enable new avenues of research, and therefore, processes which result in the ring-expansion of **1** and **2** would be useful. The first ring-expanded derivative of **1** was reported by Isobe et al.; however, the transformation was limited by the low-yielding and non-selective carbene-mediated addition of TMS-diazomethane [12].

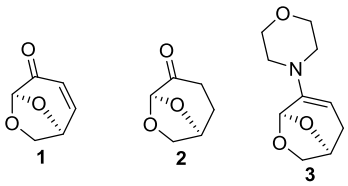

Figure 1. Levoglucosenone (**1**), Cyrene (**2**), and enamine (**3**) derived from **2**.

We have recently reported a protocol for a one-carbon homologation of **1** via the dihalocyclopropanation of enamine **3**. Subsequent ring-opening resulted in a homologated α-bromo-α,β-unsaturated ketone, an α-chloro-α,β-unsaturated ketone, or dehalogenated material [13]. There are few reports of fluorinated derivatives of 1,6-anhydrosugars such as **1** or **2** [14,15]; however, the incorporation of fluorine would be beneficial in the enantioselective synthesis of pharmaceuticals and natural products [16,17].

Enamines are known to react with difluorocarbenes to generate difluorocyclopropanes; however, subsequent ring-opening is low yielding [18]. The generation of difluorocarbenes is also challenging due to the toxic precursors and the harsh conditions required for their formation and reactions [19]. A simple procedure was recently reported by Hu, Prakash and coauthors for the generation of difluorocarbenes using readily available trifluoromethyl silane ($TMSCF_3$) to form cyclopropanes with alkenes and alkynes [20]. Herein, we report the difluorocyclopropanation of enamine **3** using these conditions, and the subsequent ring-expansion to yield a biomass-derived alkenyl fluoride.

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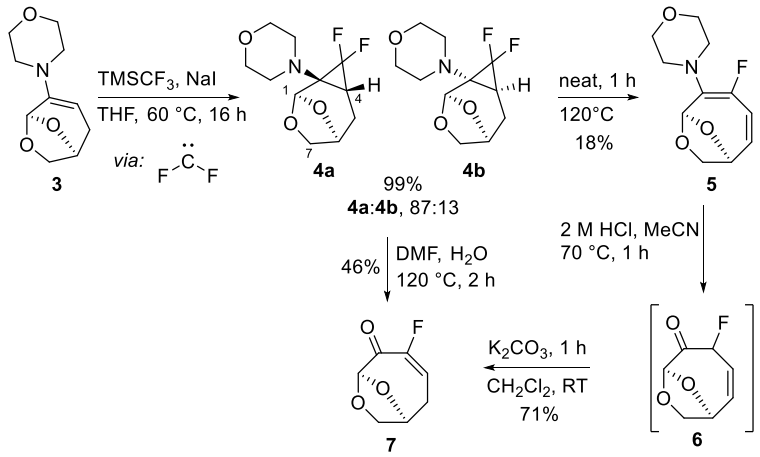
2. Results and Discussion

Enamine **3** is readily prepared from commercially available **2** by heating with a slight excess of morpholine under Dean–Stark conditions [21]. Adopting the conditions previously established for difluorocyclopropanation [20], we attempted the reaction of enamine **3** using $TMSCF_3$ and NaI as an initiator. The cyclopropanated enamine mixture **4a**/**4b** was obtained in quantitative yield without chromatography with a diastereomeric ratio of 87:13 (**4a/4b**) (Scheme 1). In the isomeric mixture, the signals for H1 at δ 5.72 and 5.88 ppm and H6 at δ 4.44 and 4.54 ppm were well resolved, which allowed for the determination of the ratio of diastereomers (Supplementary Materials). The diastereoselectivity was consistent with previous carbene additions to **3**, and the configuration was assigned based on the more favoured exo-addition of the carbene to the enamine double bond. A correlation in 1D or 2D NOE NMR between methine proton (H4) and the endo-proton of the oxymethylene bridge, which would have allowed for confirmation of the configuration, could not be detected in either isomer.



Scheme 1. Preparation of ring-expanded alkenyl fluoride **7**.

The ring-opening of dihalocyclopropanes can be promoted by heat or metal salts to yield corresponding alkenyl halide [22]. When cyclopropane **4** was heated undiluted at 120 °C under anhydrous conditions, homologated fluoroenamine **5** was isolated in 18% yield and was stable to aqueous work-up and chromatographic purification. Acidic hydrolysis of **5** was carried out at an elevated temperature to yield allylic fluoride **6**, which was identified via ^{1}H NMR spectroscopy. The treatment of intermediate **6** with K_2CO_3 produced α,β-unsaturated ketone **7** as the thermodynamic product. The overall yield for the stepwise ring-opening, hydrolysis and isomerization was 13% starting from cyclopropane **4**.

We envisaged that telescoping this reaction cascade in one pot would produce a higher yield of ring-expanded alkenyl fluoride **7**. A small series of solvents were examined for the ring-opening, with the inclusion of 1 eq. of H_2O to promote the in situ hydrolysis of intermediate **5**. Heating the mixture of cyclopropanes **4a/4b** in DMF in the presence of H_2O produced the desired ketone **7** in 46% yield in a one-pot reaction, with the liberated HF promoting the isomerization of **6** to **7**. Interestingly, under all ring-opening conditions examined, no evidence of the exocyclic alkenyl fluoride was detected in ^{1}H NMR spectra, although the lower yield could be due to decomposition via this pathway. In our previous report, the observed products after ring-opening of the corresponding dibromo- and dichlorocyclopropanes were highly sensitive to solvents or other additives [13].

In conclusion, we have demonstrated the safe and cheap difluorocyclopropanation of enamine **3** in excellent yield without any purification required. Subsequent ring-opening provided homologated ketone **7** in 46% yield starting from **3**, providing access to a fluorinated biomass-derived building block which we envisage could be useful in enantioselective synthesis.

3. Materials and Methods

3.1. General Experimental Procedure

Solvents were removed using a rotary evaporator with a bath temperature of 40 °C and pressure between 10 and 700 mbar. All solvents were distilled before use. Chemical reagents were commercially available and were used as purchased. THF was refluxed over sodium prior to use and was stored over activated 3 Å molecular sieves and in inert atmosphere. Except as indicated, reactions were magnetically stirred and monitored by NMR spectroscopy, GC-MS or thin-layer chromatography (TLC) using silica plates (silica gel 60 F254). Flash chromatography was performed on silica gel 60, using a moderate pressure applied via compressed air, and solvent mixtures are given as *v*/*v*. ^{1}H NMR was performed on a 500 MHz Bruker AVANCE III spectrometer at 298 K, and the spectra were referenced to residual solvent $CDCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded at 125 MHz and referenced to the residual solvent ($CDCl_3$, δ 77.00 ppm). ^{19}F NMR spectra were recorded at 471 MHz and referenced to the internal standard hexafluorobenzene (−164.90 ppm). NMR spectra were assigned using COSY, NOESY, HSQC, and HMBC experiments. High-resolution mass spectra were recorded using either a Waters Xevo time-of-flight or a Thermo Fisher Fusion Orbitrap mass spectrometer equipped with either an electrospray ionisation source or an atmospheric pressure chemical ionisation source, in positive or negative ionisation mode to match the preferred compound ionisation properties. Gas chromatography (GC)–MS analyses were performed using an Agilent Technologies 7890A GC-System coupled with an Agilent 5975C mass-selective detector (triple-axis detector) using an HP-5MS Agilent column (30 m Å to 250 µm Å to 0.25 µm). Operating conditions were as follows: injector—split ratio 10:1; inlet temperature—250 °C; carrier gas—helium, 1.0-mL/min, constant flow; and column temperature—50 °C (5 min hold) heated at 20 °C per minute to 250 °C (5 min hold). MS was acquired at −70 eV using a mass scan range of *m*/*z* 30–700.

3.2. Synthesis of Compounds **4a**/**4b**, **5** *and* **7**

4-((1*R*,2*R*/*S*,4*S*/*R*,6*S*)-3,3-Difluoro-8,9-dioxatricyclo[4.2.1.02,4]nonan-2-yl)morpholine (**4a**/**4b**).

To a stirred solution of **3** (1.50 g, 7.60 mmol) in dry THF (30 mL), NaI (227 mg, 1.52 mmol) and $TMSCF_3$ (2.80 mL, 19.0 mmol) were added, and the mixture was heated to 60 °C for 16 h. The mixture was diluted with satd. aqueous $NaHCO_3$ (50 mL) and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and the volatiles were removed under reduced pressure to yield a mixture of **4a** and **4b** (87:13) as an orange solid (1.87 g, 99%). mp 78–80 °C; IR $\tilde{\nu}_{max}$ 2958, 2852, 1435, 1270, 1179, 1112 cm^{-1}; Assignment of **4a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (s, 1H), 4.46–4.41 (m, 1H), 3.97 (ddd, *J* = 7.6, 6.3, 0.8 Hz, 1H), 3.70 (dd, *J* = 7.6, 2.1 Hz, 1H), 3.68–3.58 (m, 4H), 3.03–2.94 (m, 2H), 2.86–2.80 (m, 2H), 2.42–2.36 (m, 1H), 1.86 (dd, *J* = 14.5, 10.0 Hz, 1H), 1.54–1.46 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 114.1 (dd, *J* = 293.9, 284.5 Hz), 95.6 (app. t, *J* = 2.5 Hz), 70.2, 68.2, 67.6, 48.9, 47.5 (dd, *J* = 10.2, 8.6 Hz), 25.4, 21.3 (dd, *J* = 10.7, 10.2 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ −139.37 (dd, *J* = 154.3, 17.8 Hz), −149.36 (d, *J* = 154.3 Hz); HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calcd for $C_{11}H_{16}F_2NO_3^+$: 248.1093; found: 248.1091; **4b**: partial: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (s, 1H), 4.54 (dd, *J* = 7.4, 5.6 Hz, 1H), 3.51 (d, *J* = 7.1 Hz, 1H), 2.81–2.73 (m, 4H), 2.33–2.25 (m, 1H), 1.64 (d, *J* = 14.5 Hz, 1H), 1.32–1.21 (m, 1H); partial: ^{13}C NMR (125 MHz, $CDCl_3$) δ 68.0 (d, *J* = 5.5 Hz), 67.4 (d, *J* = 1.2 Hz), 67.1, 51.9 (dd, *J* = 9.3, 8.6 Hz), 48.5, 20.0, 18.5 (dd, *J* = 12.0, 9.9 Hz).

4-((1S,6R)-4-Fluoro-7,9-dioxabicyclo[4.2.1]nona-2,4-dien-5-yl)morpholine (**5**).

A mixture of cyclopropane diastereomers **4a**/**4b** (3.80 g, 15.4 mmol) was heated undiluted to 120 °C for 1 h under a constant stream of N_2. The mixture was diluted with satd. aqueous $NaHCO_3$ (50 mL), and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, the volatiles were removed under reduced pressure and the crude material was purified via flash column chromatography (petroleum ether/ethyl acetate, 3:1) to yield **5** as a yellow oil (634 mg,

18%). R_f 0.4 (petroleum ether/ethyl acetate, 2:1); $[\alpha]_D^{24}$ −165 (*c* 1.0, CH_2Cl_2); IR $\tilde{\nu}_{max}$ 2960, 2853, 1648, 1607, 1452, 1373 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.91–5.82 (m, 2H), 5.64 (d, *J* = 8.7 Hz, 1H), 4.69–4.64 (m, 1H), 4.16 (dd, *J* = 7.4, 2.4 Hz, 1H), 3.96 (dd, *J* = 7.4, 6.0 Hz, 1H), 3.76–3.65 (m, 4H), 3.18–3.10 (m, 2H), 3.09–3.03 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.3 (d, *J* = 234.6 Hz), 134.3 (d, *J* = 9.3 Hz), 128.8 (d, *J* = 13.9 Hz), 123.4 (d, *J* = 41.9 Hz), 102.0 (d, *J* = 9.8 Hz), 76.8, 73.4, 67.3 (d, *J* = 1.5 Hz), 50.5 (d, *J* = 5.7 Hz); HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calcd for $C_{11}H_{15}FNO_3^+$: 228.1030; found: 228.1030.

(1*S*,6*R*)-4-Fluoro-7,9-dioxabicyclo[4.2.1]non-3-en-5-one (**7**).

Synthesis from **4a**/**4b**: To a mixture of cyclopropane diastereomers **4a**/**4b** (420 mg, 1.70 mmol) in DMF (1 mL), H_2O (0.03 mL, 1.70 mmol) was added, and the mixture was heated to 120 °C for 2 h under a constant stream of N_2. The mixture was diluted with satd. aqueous $NaHCO_3$ (20 mL), and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, the volatiles were removed under reduced pressure and the crude material was purified via flash column chromatography (petroleum ether/ethyl acetate, 2:1) to yield **7** as a yellow solid (125 mg, 46%). R_f 0.3 (petroleum ether/ethyl acetate, 2:1); mp 39–41 °C; $[\alpha]_D^{22}$ +65 (*c* 1.0, CH_2Cl_2); IR $\tilde{\nu}_{max}$ 2962, 2909, 1689, 1653, 1223 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.14 (dddd, *J* = 21.9, 6.5, 3.3, 0.8 Hz, 1H), 5.42 (d, *J* = 6.9 Hz, 1H), 4.84–4.77 (m, 1H), 4.19–4.14 (m, 1H), 3.89 (dd, *J* = 7.8, 3.7 Hz, 1H), 3.07–2.98 (m, 1H), 2.41 (dddd, *J* = 19.9, 6.5, 3.8, 1.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.8 (d, *J* = 22.2 Hz), 152.1 (d, *J* = 251.2 Hz), 117.7 (d, *J* = 23.5 Hz), 102.3 (d, *J* = 4.0 Hz), 73.5, 68.7, 32.2 (d, *J* = 7.9 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ −123.2; HRMS (ESI-TOF) *m*/*z*: $[M+H]^+$ calcd for $C_7H_8FO_3^+$: 159.0452; found: 159.0452.

Synthesis from **5**: To a mixture of enamine **5** (154 mg) in MeCN (4 mL), 2 M HCl (4 mL) was added, and the mixture was heated to 70 °C for 1 h. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried over Na_2SO_4, and solid K_2CO_3 (2 g) was added and the suspension was stirred for 1 h at RT. The mixture was filtered and the volatiles removed under reduced pressure to yield **7** as a yellow solid (76 mg, 71%).

Supplementary Materials: Images of ^1H, ^{13}C and ^{19}F NMR spectra for new compounds reported in this article.

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Conflicts of Interest: The authors declare no conflicts of interest.

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