



Cite this: *RSC Adv.*, 2023, 13, 30777

Received 21st July 2023  
Accepted 2nd October 2023

DOI: 10.1039/d3ra04937j

rsc.li/rsc-advances

# Cobalt-assisted route to rare carbocyclic C-ribonucleosides†

A. C. Ojeda-Porras, V. Roy,\* O. Bourzikat, P. Favetta and L. A. Agrofoglio \*

(Re)emerging RNA viruses have been major threats to public health in the past years, and from the few drugs available, nucleoside analogues are still at the cornerstone of the antiviral therapy. Among them, the synthesis of carbocyclic C-nucleosides is suffering from long syntheses and poor yields. Herein we report a concise stereoselective synthesis of rare carbocyclic C-nucleosides (**11a–l**) bearing non-canonical nucleobases through a cobalt-assisted-route as key step starting from the optically pure (–)-cyclopentenone **1**. This approach paves the route for novel carbocyclic C-nucleoside discovery.

## Introduction

The continuous growth of the human population as well as human interaction with wild environments have shown several emerging and re-emerging RNA viruses responsible of highly fatal viral diseases and threatened public health with deadly outbreaks of global concern,<sup>1–4</sup> the majority of RNA viruses are zoonotic or vector-borne infectious agents<sup>5–7</sup> and are considered as the most common class of pathogens (2 to 3 novel viruses discovered by year);<sup>8</sup> they represent a challenge for global disease control<sup>9</sup> because of their faster evolutionary rates and increased mutability compared to some DNA viruses.<sup>10</sup> Except for the SARS-CoV-2 for which vaccines have been developed at an unprecedented speed, the biological diversity and rapid adaptive rates of RNA viruses make that no effective commercial vaccine is available for any of the above-mentioned viruses, and we are still awaiting the first effective antiviral drugs to be approved. Nucleoside analogues, with more than 40 derivatives marketed to treat viral DNA infections as well as certain cancers or bacterial infections,<sup>11</sup> are the most promising and leading-class of antivirals against RNA emerging viruses.<sup>12</sup> On one hand, the replacement of the oxygen in the furanose ring with methylene group led to carbocyclic nucleosides which are chemically more stable towards the enzymatic cleavage of the *N*-glycosidic bond and have an increased cell permeability because of its higher lipophilicity than their nucleoside parents. The broad spectrum of biological activities of carbocyclic nucleosides and their pharmaceutical importance have generated considerable research interest in their design and synthesis. Many reviews by us<sup>13</sup> and others<sup>14</sup> have been published on this topic, as well as on their biological applications.<sup>15</sup>

On the other hand, C-nucleosides,<sup>16</sup> in which the ribofuranosyl moiety is linked to a heterocyclic non-canonical base (such as bearing hydrophobic aryl group)<sup>17</sup> through a C–C bond instead of C–N-bond found in natural nucleosides, have been reported for their antiviral and/or anticancer potential. So far, no natural carbocyclic C-nucleosides have been found in nature and only a few have been synthesized to date (Fig. 1), such as the inhibitor of histone methyltransferase DOT1L recently developed by Paruch *et al.*,<sup>18</sup> the carbocyclic formycin<sup>19</sup> analog by Leahy *et al.*, and the compound reported by Fletcher *et al.*<sup>20</sup> bearing a difluoro pyridine non-canonical nucleobase.

A first approach was reported in 2001 by Chu and co-workers<sup>21</sup> from 1,4-γ-ribonolactone as chiral starting material (Scheme 1A). The key intermediate is obtained by Bu<sub>3</sub>SnH–AIBN reduction of an olefinic intermediate obtained by treating the protected ribonolactone with ethyl cyanoacetate and *t*BuOK and then it is converted to final carbocyclic C-nucleosides by the full construction of the pyrazole non-canonical nucleobases.

Paruch and co-workers developed a diastereoselective, racemic procedure from norbornadiene through the TIPS-protected cyclopentanone which underwent diastereoselective addition of various lithiated (hetero)aryl moieties (Scheme 1B).<sup>22</sup> A recent publication by Fletcher group<sup>20</sup> reported the Rh-catalytic asymmetric synthesis of carbocyclic C-nucleosides using an asymmetric Suzuki–Miyaura type reaction as the key C–C bond forming step, followed by late-stage addition of the hydroxymethyl group to ribose analogs (Scheme 1C).

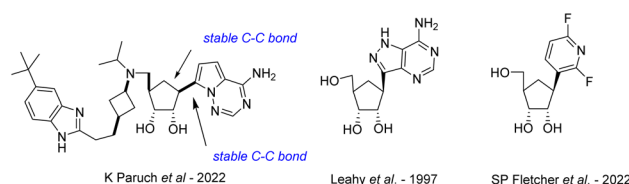
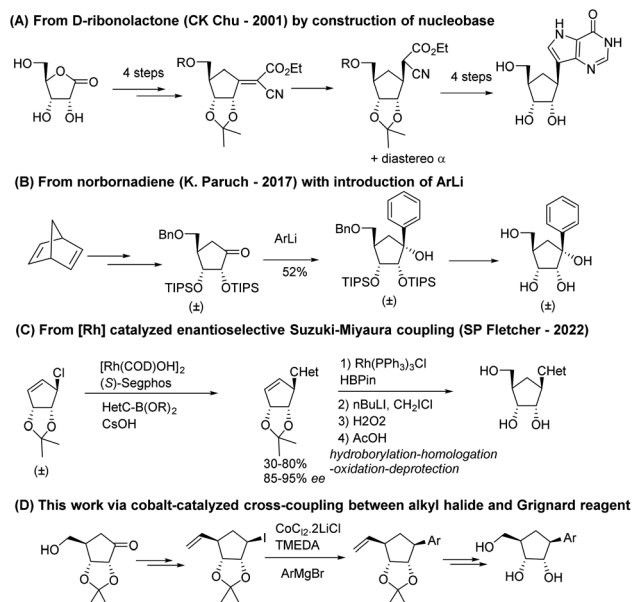


Fig. 1 Structure of synthetic carbocyclic C-nucleosides.

Université d'Orléans et CNRS, ICOA, UMR 7311, F-45067, Orléans, France. E-mail: luigi.agrofoglio@univ-orleans.fr

† Electronic supplementary information (ESI) available: <sup>1</sup>H, <sup>13</sup>C data of selected compounds. See DOI: <https://doi.org/10.1039/d3ra04937j>





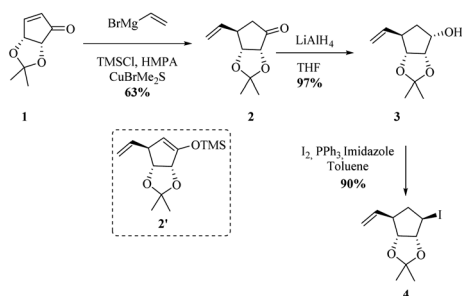
Scheme 1 Comparison of previous syntheses and our synthesis of carbocyclic C-ribose nucleosides.

Even if several efforts towards the synthesis of enantio-enriched carbocyclic nucleosides have been reported in the past years, the multi-step sequences combined with the difficulty associated to the installation of stereocenters make these approaches long, tedious, and not suitable for the pharmaceutical industry. Thus, the synthetic difficulties have probably hampered the production of those very promising carbocyclic C-nucleoside analogs.

Hence, we focused on designing a new, versatile, robust and stereo-controlled synthetic route to diverse carbocyclic C-nucleosides without the use chiral catalyst but taking advantage of stereocenters previously set in the molecule (Scheme 1D). Several non-canonical aromatic bases were installed.<sup>23</sup> This (hetero)aryl moieties included electron-donating and electron-withdrawing substituents, and the presence of heteroatoms in the ring, while maintaining  $\pi$ -stacking and Watson-Crick hydrogen bond interactions.

## Results and discussion

We began the synthesis from the commercially available optically pure (–)-cyclopentenone **1** which is easily obtained in 3



Scheme 2 Synthesis of enantiomerically pure halohydrin **4**.

steps from D-ribose.<sup>24</sup> Following a reported procedure by Schneller *et al.*,<sup>25a</sup> the diastereoselective Grignard addition of vinyl magnesium<sup>25b</sup> bromide on **1** afforded the ketone **2** as one diastereomer in 63% yield (Scheme 2). <sup>1</sup>H NMR and NOESY experiments revealed that H<sub>3</sub> correlates only with H<sub>2</sub> ( $d, J(\text{H}_3, \text{H}_2) = 5.2$  Hz) and not with H<sub>4</sub> corresponding to a dihedral angle close to 90° according to Karplus equation. This angle is attainable with H<sub>3</sub> and H<sub>4</sub> *trans* to each other (but not when they are *cis*), proving that the vinyl substituent of the organocuprate added to the less hindered face resulting in **2** with the depicted stereochemistry, as illustrated by molecular models (see ESI†). The use of TBAF in the quenching of the Grignard addition step is vital since the yield of **2** can be negatively affected by the formation and isolation of silyl ether **2'**. Reduction of resulting cyclopentanone **2** with  $\text{AlLiH}_4$  afforded alcohol **3** in 97% yield. The compound was diastereomerically pure according to <sup>1</sup>H and <sup>13</sup>C NMR. <sup>1</sup>H NMR and NOESY analysis, and Karplus equation indicate that compound **3** has H<sub>1</sub> and H<sub>2</sub> in a *cis* relationship.<sup>25b</sup> This is in agreement with molecular models (see ESI†). With alcohol **3** in hand, an Appel-type reaction (proceeding with the inversion of configuration) using iodine and triphenylphosphine in the presence of imidazole was intended. This reaction was initially performed using dichloromethane as solvent, but unfortunately, just starting material was recovered. Finally when toluene was used as solvent and the reaction was done under reflux conditions, the desired iodohydrin **4** was obtained in 90% yield. Interestingly, <sup>1</sup>H NMR clearly shows a van der Waals deshielding effect of the iodine atom on the vinylic C–H proton.

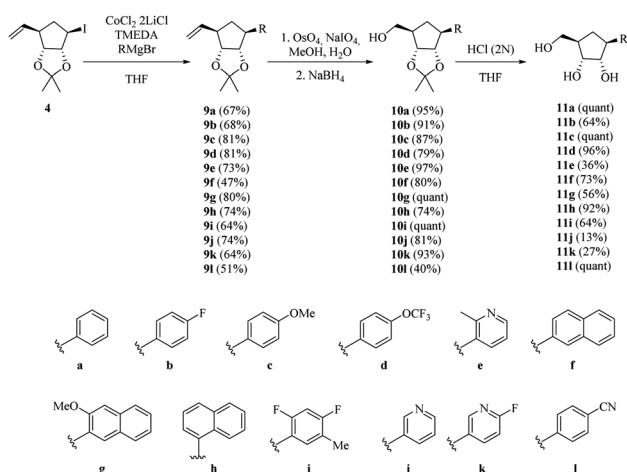
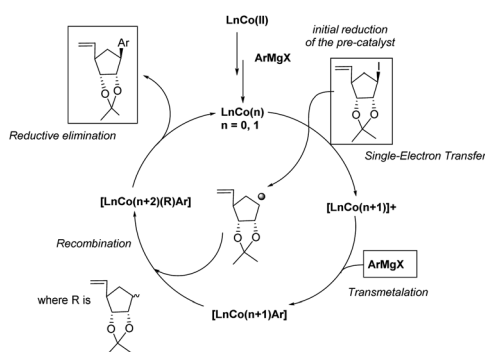
Inspired by the cobalt-mediated diastereoselective cross coupling reaction reported by Knochel and co-workers,<sup>26</sup> we decided to apply this methodology as key step of the synthesis of carbocyclic C-nucleosides. According to the authors, the presence of the neighbouring TBS-ether group is responsible for the high diastereoselectivity observed because the silyl ether and the newly inserted aromatic group adopt an anti-configuration. We sought the isopropylidene motive at C2–C3 would have a similar effect by blocking the  $\alpha$ -phase of the cyclopentane nucleoside. The cobalt solution can be prepared in a day using the protocol reported by Knochel. Before trying the conditions in the previously synthesized iodohydrin **4**, we decided to test them on the model substrate **7** (Scheme 3). Starting from epoxide **5**, iodohydrin **6** was obtained in 72% yield. Further protection of the alcohol as a TBS ether afforded the model substrate **7** in 84% yield as a racemate.

With **7** in hand, we tested the cobalt-catalysed cross coupling conditions. Thus, to a cooled solution of the iodohydrin **7** and TMEDA in dry THF was slowly added the Grignard reagent. To our delight, we were able to isolate the desired compound **8** in 88% yield as only relative *trans* stereochemistry, when the



Scheme 3 Cobalt-assisted cross-coupling on a model compound.



Scheme 4 Synthesis of carbocyclic C-nucleosides **11a-l**.Scheme 5 Proposed mechanism (adapted from Guérinot and Cossy<sup>27</sup>).

reaction was allowed to stir at room temperature overnight. The aryl group was *trans* to the silylated ether. We did notice that shorter reaction times resulted in a decreased reaction yield.

We then applied the above-mentioned conditions for the cross-coupling reaction between halohydrin **4** and different Grignard reagents (Scheme 4). The desired products (**9a-l**) were obtained in good yields in the presence of activating groups, such as methoxide **9c** and trifluoro-methoxide **9d**. Fluorinated compound **9b** was isolated in 68% yield. Ortho-substituted product **9e** was successfully obtained in moderate yield despite its steric hindrance and the presence of a nitrogenated base.

Binaphthyl substituted products **9f-h** were also isolated, although in poor to moderate yields. Only one isomer is produced and its formation proceeds through a proposed radical mechanism (Scheme 5).<sup>27</sup>

With alkenes **9a-l** in hand, an oxidative cleavage of the double bond was attempted. Initially, a ruthenium catalysed reaction was performed on **9a** furnishing **10a** in just 25% yield. To our delight, the use of osmium tetroxide afforded alcohols **10a-l** in excellent yields (Scheme 4). Later deprotection of the isopropylidene ketal in acidic media yielded the desired carbocyclic C-nucleoside analogues **11a-l**. It should be noticed

that the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of **11a** are consistent with those reported by Fletcher *et al.* for the same compound obtained by a different way.<sup>20</sup>

## Conclusions

In summary, a series of hitherto unknown rare carbocyclic C-nucleosides (**11a-l**) were successfully synthesized in a highly efficient manner from protected ribonolactone **1** through a cobalt-catalyzed cross-coupling between the enantiopure halohydrin **4** and various aryl Grignard reagents. To the best of our knowledge, the proposed synthetic procedure is far superior to any other route reported to date. It is believed that this study will contribute to explore this promising class of carbocyclic C-nucleosides.

## Experimental section

### General methods

Commercially available chemicals were of reagent grade and used as received. The reactions were monitored by thin layer chromatography (TLC) analysis using silica gel plates (Kieselgel 60F254, E. Merck). Column chromatography was performed on Silica Gel 60 M (0.040  $\times$  0.063 mm, E. Merck). Optical rotations were measured with a PerkinElmer 341 polarimeter in appropriate solvent, at the indicated temperature (20  $^\circ\text{C}$ ) and at 589 nm sodium line, in a 1 dm cell. Concentrations are given in g/100 mL. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Varian InovaUnity 400 spectrometer (400 MHz) in ( $d_4$ ) methanol,  $\text{CDCl}_3$ , shift values in parts per million relative to  $\text{SiMe}_4$  as internal reference. High Resolution Mass spectra were performed on a Bruker maXis mass spectrometer by the "Federation de Recherche" ICOA/CBM (FR2708) platform.

### Preparation of the $\text{CoCl}_2 \cdot 2\text{LiCl}$ (1.0 M) solution in THF

The  $\text{CoCl}_2 \cdot 2\text{LiCl}$  (1.0 M) solution in THF was prepared following the reported experimental procedure.<sup>24</sup> A dried two neck 50 mL flask equipped with a stirring bar a septum was charged with anhydrous LiCl (2.12 g) and heated at 130  $^\circ\text{C}$  under high vacuum for 2 h. After cooling to room temperature under argon,  $\text{CoCl}_2$  (3.24 g) was added. The resulting mixture was heated to 130  $^\circ\text{C}$  for 5 h under high vacuum, cooled down to room temperature under argon and charged with dry THF (25 mL). The resulting solution was vigorously stirred at room temperature overnight. The dark blue solution was used within 1 month.

### Synthesis of Grignard reagents

All non-commercially available aryl Grignard reagents were prepared following the following experimental procedure. To a flask containing a stirring bar was added Mg turnings (240 mg, 10 mmol, 2.0 equiv.) and LiCl (230 mg, 5.5 mmol, 1.1 equiv.). The flask was flame dried under vacuum and flushed with argon three times. THF (5 mL) and dibromoethane (25  $\mu\text{L}$ ) were then added, followed by the dropwise addition of 1-bromo-4-methoxybenzene (935 mg, 5 mmol). The resulting solution



was stirred at room temperature for two hours and used immediately in the cross coupling reaction.

### General procedure A: cobalt mediated cross coupling reaction

To a stirred solution of iodohydrin (1.0 equiv.) in dry THF (1 M) was added TMEDA (0.3 equiv.) and a 1.0 M solution of  $\text{CoCl}_2 \cdot 2\text{LiCl}$  in THF (0.85 equiv.). The resulting blue solution was cooled down to  $-78^\circ\text{C}$  before the Grignard reagent (1.7 equiv.) was slowly added. The reaction mixture was stirred at room temperature overnight. A saturated aqueous solution of  $\text{NH}_4\text{Cl}$  was added to quench the reaction. The aqueous layer was extracted with  $\text{AcOEt}$ , and the combined organic extracts were washed with brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography to afford the desired product.

### General procedure B: oxidative cleavage of double bond catalysed by osmium

To a stirred solution of alkene (1.0 equiv.) in a mixture of methanol: water (7 : 3) (0.11 M) was added  $\text{NaIO}_4$  (2.07 equiv.). The reaction mixture was cooled down to  $0^\circ\text{C}$  and a 2.5 wt% solution of  $\text{OsO}_4$  in *t*-BuOH (0.08 equiv.) was slowly added. The resulting mixture was stirred 1 h at  $0^\circ\text{C}$  and 2 h at room temperature. The newly formed white solid was removed by filtration and washed with a mixture of methanol water (2 : 1). The filtrate was then cooled down to  $0^\circ\text{C}$  and  $\text{NaBH}_4$  (6.4 equiv.) was added portion wise, turning the reaction black. The resulting mixture was allowed to stir at room temperature for 30 minutes, after which the volatiles were removed under reduced pressure. Brine was then added and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic extracts were washed with brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure afford the desired product.

### General procedure C: deprotection of the isopropylidene acetal

To a stirred solution of isopropylidene acetal (1.0 equiv.) in THF (0.4 M) at  $0^\circ\text{C}$  was added dropwise a 2.0 M aqueous solution of  $\text{HCl}$  (0.2 M final concentration). The reaction mixture was stirred at room temperature for 16 h. The resulting solution was neutralized by the addition of a saturated aqueous solution of  $\text{NaHCO}_3$ . The aqueous layer was abundantly extracted with  $\text{AcOEt}$ , and the combined organic extracts were washed with brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to afford the desired product.

**(3aR,6aR)-2,2-Dimethyl-3a,6a-dihydro-4H-cyclopenta[d][1,3]dioxol-4-one (1).** Commercially available ketone **8** was purified by flash chromatography using petroleum ether:  $\text{AcOEt}$  to afford the desired product **1** as a white solid (109 mg, 84% yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 7.57–7.63 (m, 1H), 6.21 (d,  $J = 5.9$  Hz, 1H), 5.34–5.18 (m, 1H), 4.46 (d,  $J = 5.5$  Hz, 1H), 1.41 (s, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 202.9, 159.5, 134.3, 115.6, 78.6, 76.5, 27.4, 26.2.

**(3aR,6R,6aR)-2,2-Dimethyl-6-vinyltetrahydro-4H-cyclopenta[d][1,3]dioxol-4-one (2).** To a stirred suspension of  $\text{CuBrS} \cdot \text{Me}_2\text{S}$  (612 mg, 2.98 mmol, 0.1 equiv.) in dry THF (13.5 mL) at  $-78^\circ\text{C}$  was added a solution of vinyl magnesium bromide (1.0 M in THF) (90 mL, 90 mmol, 3.0 equiv.) dropwise. The resulting mixture was allowed to stir at this temperature for 10 minutes before a solution of ketone **1** (4.59 g, 29.8 mmol),  $\text{TMSCl}$  (7.75 mL, 60.8 mmol, 2.05 equiv.) and  $\text{HMPA}$  (13.5 mL, 77.5 mmol, 2.6 equiv.) in dry THF (14.8 mL) was slowly added. The reaction mixture was stirred at  $-78^\circ\text{C}$  for 5 h. A saturated aqueous solution of  $\text{NH}_4\text{Cl}$  and 10 mL of TBAF were added to quench the reaction. The resulting mixture was allowed to stir at room temperature for 30 min. The aqueous layer was extracted with  $\text{AcOEt}$ , and the combined organic extracts were washed with brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:  $\text{AcOEt}$  (5 : 1) to afford the desired product **2** as a pale yellow oil (3.54 g, 65% yield).  $^{25a}$   $[\alpha]_D^{20} = -95.1$  ( $c = 1.2$ ,  $\text{CH}_3\text{OH}$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 5.83 (ddd,  $J = 17.2, 10.6, 6.5$  Hz, 1H), 5.20–5.02 (m, 2H), 4.64 (d,  $J = 5.2$  Hz, 1H), 4.20 (d,  $J = 5.2$  Hz, 1H), 3.11 (t,  $J = 7.3$  Hz, 1H), 2.83 (dd,  $J = 18.3, 8.6$  Hz, 1H), 2.28 (d,  $J = 18.3$  Hz, 1H), 1.44 (s, 3H), 1.35 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 213.2, 137.1, 116.4, 112.4, 81.4, 77.9, 39.8, 38.6, 26.9, 24.9.

**(3aS,4S,6R,6aR)-2,2-Dimethyl-6-vinyltetrahydro-4H-cyclopenta[d][1,3]dioxol-4-ol (3).** To a stirred suspension of  $\text{LiAlH}_4$  (1.23 g, 32.2 mmol, 1.7 equiv.) in dry THF (48 mL) at  $-78^\circ\text{C}$  was slowly added a solution of ketone **2** (3.46 g, 18.9 mmol) in dry THF (32 mL). The reaction mixture was stirred at room temperature for 2 h. A saturated aqueous solution of Rochelle salt was slowly added to quench the reaction and the resulting mixture was allowed to stir at room temperature overnight. The aqueous layer was extracted with  $\text{AcOEt}$ , and the combined organic extracts were washed with brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to afford the desired product **3** as a colourless oil (3.40 g, 97% yield).  $^{25a}$   $[\alpha]_D^{20} = +44.4$  ( $c = 1.20$ ,  $\text{CH}_3\text{OH}$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 5.74 (ddd,  $J = 17.2, 10.5, 6.5$  Hz, 1H), 5.10–5.04 (m, 2H), 4.51–4.45 (m, 2H), 4.07 (bs, 1H), 2.78–2.69 (m, 1H), 2.42 (d,  $J = 7.5$  Hz, 1H  $\text{D}_2\text{O}$  exchangeable), 1.95–1.84 (m, 2H), 1.51 (s, 3H), 1.35 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 138.0, 115.3, 111.6, 84.3, 79.0, 71.1, 44.3, 36.0, 26.1, 24.3.

**(3aR,4R,6R,6aR)-4-Iodo-2,2-dimethyl-6-vinyltetrahydro-4H-cyclopenta[d][1,3]dioxole (4).** To a stirred solution of alcohol **3** (3.40 g, 18.5 mmol) in toluene (645 mL) was added triphenyl phosphine (14.5 g 55.4 mmol, 3.0 equiv.), imidazole (3.77 g, 55.4 mmol, 3.0 equiv.) and iodine (9.37 g, 36.9 mmol, 2.0 equiv.). The reaction mixture was refluxed for 2 h and then cooled down to room temperature. The resulting mixture was diluted with  $\text{AcOEt}$  and washed with a saturated aqueous solution of  $\text{NaHCO}_3$ . The organic phase was washed with brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether:  $\text{CH}_2\text{Cl}_2$  (8 : 2) to (1 : 1) to afford the desired product **4** as a pale yellow solid (4.67 g, 86% yield).  $[\alpha]_D^{20} = -2.7$  ( $c = 0.60$ ,  $\text{CH}_3\text{OH}$ ).  $^1\text{H}$  NMR (400 MHz,





$\text{CDCl}_3$ )  $\delta$  ppm: 5.97 (ddd,  $J = 17.2, 10.3, 6.9$  Hz, 1H), 5.15–5.05 (m, 2H), 4.97–4.81 (m, 1H), 4.41 (dd,  $J = 6.7, 4.0$  Hz, 1H), 4.11–3.98 (m, 1H), 2.77–2.57 (m, 2H), 2.05–2.13 (m, 1H), 1.50 (s, 3H), 1.30 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 138.1, 115.8, 113.2, 90.5, 85.4, 49.9, 43.2, 27.3, 24.9, 24.8. HRMS (ESI): calcd for  $\text{C}_{10}\text{H}_{16}\text{IO}_2^+ [\text{M} + \text{H}]^+$ , 295.0189; found, 295.0190.

**2-Iodocyclopentan-1-ol (6).** To a stirred solution of  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (1.07 g, 2.89 mmol, 0.5 equiv.) and NaI (865 mg, 5.75 mmol, 1.0 equiv.) in acetonitrile (57 mL) was added dropwise a solution of epoxide 5 (483 mg, 5.75 mmol) in acetonitrile (11 mL). The reaction mixture was protected from the light and stirred at room temperature for 24 h. The volatiles were removed under reduced pressure and the resulting mixture was diluted with AcOEt. The organic phase was washed with brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using  $\text{CH}_2\text{Cl}_2$  to afford the desired product 6 as a pale yellow oil (876 mg, 72% yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 4.46 (bs, 1H), 4.06–4.02 (m, 1H), 2.41–2.32 (m, 1H), 2.14–2.05 (m, 2H), 1.96 (s, 1H), 1.88–1.77 (m, 2H), 1.63–1.58 (m, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 82.2, 35.6, 34.1, 31.0, 22.0.

**( $\pm$ )-tert-Butyl((2-iodocyclopentyl)oxy)dimethylsilane (7).** To a stirred solution of alcohol 6 (87 mg, 0.41 mmol) in dry DMF (2.0 mL) was added imidazole (130 mg, 1.62 mmol, 3.9 equiv.) and TBDMSCl (185 mg, 1.35 mmol, 3 equiv.). The reaction mixture was stirred at room temperature for 3 h and 30 min. The resulting mixture was diluted with  $\text{CH}_2\text{Cl}_2$  and the organic phase was washed several times with an aqueous solution of LiCl, then washed with brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography using petroleum ether to afford the desired product 7 as a pale yellow oil (109 mg, 84% yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 4.46–4.37 (m, 1H), 4.07–3.95 (m, 1H), 2.25–2.41 (m, 1H), 1.99–2.12 (m, 2H), 1.85–1.72 (m, 2H), 1.61–1.47 (m, 1H), 0.88 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 82.5, 35.8, 35.0, 32.3, 25.8, 22.3, 18.0, –4.5, –4.8.

**( $\pm$ )-tert-Butyldimethyl((2-phenylcyclopentyl)oxy)silane (8).** Following the general procedure A for iodohydrin 7 (163 mg, 0.5 mmol), the desired compound 8 (122 mg, 88% yield) was isolated as a colourless oil after purification by flash chromatography using petroleum ether.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 7.38–7.15 (m, 5H), 4.07 (q,  $J = 7.0$  Hz, 1H), 2.92 (dd,  $J = 16.6, 8.1$  Hz, 1H), 2.20–1.98 (m, 2H), 1.95–1.75 (m, 3H), 1.74–1.64 (m, 1H), 0.83 (s, 9H), –0.14 (s,  $J = 19.0$  Hz, 3H), –0.19 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 144.0, 128.1, 127.6, 126.0, 81.6, 54.4, 34.8, 30.9, 25.8, 21.9, 18.0, –5.0.

**(3aS,4S,6R,6aR)-2,2-Dimethyl-4-phenyl-6-vinyltetrahydro-4H-cyclopenta[d][1,3]dioxole (9a).** Following the general procedure A for iodohydrin 4 (700 mg, 2.35 mmol), the desired compound 9a (360 mg, 63% yield) was isolated as a colourless oil after purification by flash chromatography using petroleum ether:  $\text{CH}_2\text{Cl}_2$  (7 : 3) to (1 : 1).  $[\alpha]_{\text{D}}^{20} = -8.4$  ( $c = 15.3$ ,  $\text{CH}_3\text{OH}$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 7.37–7.23 (m, 5H), 5.96 (ddd,  $J = 17.3, 10.3, 7.1$  Hz, 1H), 5.28–5.10 (m, 2H), 4.61–4.57 (m, 1H), 4.49–4.43 (m, 1H), 3.27 (dt,  $J = 12.6, 6.3$  Hz, 1H), 2.81 (td,  $J = 12.7, 6.3$  Hz, 1H), 2.36 (dt,  $J = 12.7, 6.3$  Hz, 1H), 1.87–1.76 (m,

1H), 1.61 (s, 3H), 1.35 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 142.3, 139.0, 128.5, 127.1, 126.5, 115.2, 113.4, 87.0, 85.3, 50.5, 49.5, 38.4, 27.7, 25.2. HRMS (ESI): calcd for  $\text{C}_{16}\text{H}_{21}\text{O}_2^+ [\text{M} + \text{H}]^+$ , 245.1536; found, 245.1535.

**(3aS,4S,6R,6aR)-4-(4-Fluorophenyl)-2,2-dimethyl-6-vinyl-tetrahydro-4H-cyclopenta[d][1,3]dioxole (9b).** Following the general procedure A for iodohydrin 4 (231 mg, 0.78 mmol), the desired compound 9b (135 mg, 68% yield) was isolated as a colourless oil after purification by flash chromatography using petroleum ether:  $\text{CH}_2\text{Cl}_2$  (1 : 2).  $[\alpha]_{\text{D}}^{20} = -22.9$  ( $c = 5.10$ ,  $\text{CH}_3\text{OH}$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 7.29–7.23 (m, 2H), 6.99–7.06 (m, 2H), 6.02–5.87 (m, 1H), 5.20 (d,  $J = 17.2$  Hz, 1H), 5.11 (d,  $J = 10.4$  Hz, 1H), 4.54–4.40 (m, 2H), 3.31–3.16 (m, 1H), 2.81–2.76 (m, 1H), 2.36–2.31 (m, 1H), 1.83–1.69 (m, 1H), 1.60 (s, 3H), 1.34 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 161.6 (d,  $J = 245$  Hz), 138.8, 137.9 (d,  $J = 3.03$  Hz), 128.5 (d,  $J = 7.07$  Hz), 115.3, 115.2 (d,  $J = 21.2$ ), 113.5, 87.0, 85.2, 49.9, 49.3, 38.4, 27.6, 25.1.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: –116.69. HRMS (ESI): calcd for  $\text{C}_{16}\text{H}_{20}\text{FO}_2^+ [\text{M} + \text{H}]^+$ , 263.1442; found, 263.1443.

**(3aS,4S,6R,6aR)-4-(4-Methoxyphenyl)-2,2-dimethyl-6-vinyl-tetrahydro-4H-cyclopenta[d][1,3]dioxole (9c).** Following the general procedure A for iodohydrin 4 (294 mg, 1.0 mmol), the desired compound 9c (222 mg, 81% yield) was isolated as a white solid after purification by flash chromatography using petroleum ether:  $\text{CH}_2\text{Cl}_2$  (6 : 4) to (4 : 6).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 7.19 (d,  $J = 8.5$  Hz, 2H), 6.86 (d,  $J = 8.4$  Hz, 2H), 5.92 (ddd,  $J = 17.3, 10.3, 7.1$  Hz, 1H), 5.19–5.07 (m, 2H), 4.52–4.49 (m, 1H), 4.43–4.39 (m, 1H), 3.79 (s, 3H), 3.19 (dt,  $J = 12.6, 6.2$  Hz, 1H), 2.81–2.69 (m, 1H), 2.35–2.25 (m, 1H), 1.79–1.71 (m, 1H), 1.57 (s, 3H), 1.31 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 158.3, 139.0, 134.4, 128.0, 115.1, 113.9, 113.3, 87.2, 85.3, 55.3, 49.7, 49.5, 38.6, 27.7, 25.1. HRMS (ESI): calcd for  $\text{C}_{17}\text{H}_{23}\text{O}_3^+ [\text{M} + \text{H}]^+$ , 275.1645; found, 275.1642.  $[\alpha]_{\text{D}}^{20} = 18.23$  ( $c = 1.0$ ,  $\text{CH}_2\text{Cl}_2$ ).

**(3aS,4S,6R,6aR)-2,2-Dimethyl-4-(4-(trifluoromethoxy)phenyl)-6-vinyltetrahydro-4H-cyclopenta[d][1,3]dioxole (9d).** Following the general procedure A for iodohydrin 4 (294 mg, 1.0 mmol), the desired compound 9d (265 mg, 81% yield) was isolated as a white solid after purification by flash chromatography using petroleum ether:  $\text{CH}_2\text{Cl}_2$  (7 : 3) to (1 : 1).  $[\alpha]_{\text{D}}^{20} = -43.5$  ( $c = 1.40$ ,  $\text{CH}_3\text{OH}$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 7.40–7.14 (m, 4H), 5.95 (ddd,  $J = 17.3, 10.3, 7.2$  Hz, 1H), 5.20 (d,  $J = 17.8$  Hz, 1H), 5.12 (d,  $J = 10.3$  Hz, 1H), 4.44–4.58 (m, 2H), 3.25 (dt,  $J = 12.7, 6.3$  Hz, 1H), 2.83–2.78 (m, 1H), 2.38–2.33 (m, 1H), 1.87–1.70 (m, 1H), 1.60 (s, 3H), 1.34 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 147.8 (q,  $J = 147$  Hz), 141.0, 138.7, 128.4, 121.1, 120.5 (q,  $J = 258$  Hz), 115.3, 113.6, 86.9, 85.2, 50.0, 49.3, 38.2, 27.6, 25.1.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: –57.95. HRMS (ESI): calcd for  $\text{C}_{17}\text{H}_{20}\text{F}_3\text{O}_3^+ [\text{M} + \text{H}]^+$ , 329.1359; found, 329.1361.

**3-((3aS,4S,6R,6aR)-2,2-Dimethyl-6-vinyltetrahydro-4H-cyclopenta[d][1,3]dioxol-4-yl)-2-methylpyridine (9e).** Following the general procedure A for iodohydrin 4 (294 mg, 1.0 mmol), the desired compound 9e (190 mg, 73% yield) was isolated as a colourless oil after purification by flash chromatography using petroleum ether: AcOEt:  $\text{Et}_3\text{N}$  (9 : 1 : 0.1) to (8 : 2 : 0.1).  $[\alpha]_{\text{D}}^{20} = -3.7$  ( $c = 5.30$ ,  $\text{CH}_3\text{OH}$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 8.35 (d,  $J = 4.6$  Hz, 1H), 7.47 (d,  $J = 7.8$  Hz, 1H), 7.14–7.07 (m, 1H),



5.91 (ddd,  $J = 17.1, 9.7, 7.4$  Hz, 1H), 5.17 (d,  $J = 17.2$  Hz, 1H), 5.09 (d,  $J = 10.3$  Hz, 1H), 4.56–5.50 (m, 1H), 4.47–4.42 (m, 1H), 3.45 (dt,  $J = 12.3, 6.1$  Hz, 1H), 2.84–2.78 (m, 1H), 2.65 (s, 3H), 2.29–2.21 (m, 1H), 1.79–1.67 (m, 1H), 1.57 (s, 3H), 1.29 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 157.2, 146.9, 138.6, 135.6, 133.3, 121.3, 115.4, 113.4, 86.8, 85.2, 49.6, 46.4, 38.2, 27.7, 25.2, 22.9. HRMS (ESI): calcd for  $\text{C}_{16}\text{H}_{22}\text{NO}_2^+$  [ $\text{M} + \text{H}$ ] $^+$ , 260.1645; found, 260.1649.

**(3aS,4S,6R,6aR)-2,2-Dimethyl-4-(naphthalen-2-yl)-6-vinyl-tetrahydro-4H-cyclopenta[ $d$ ][1,3]dioxole (9f).** Following the general procedure A for iodohydrin 4 (294 mg, 1.0 mmol), the desired compound 9f (138 mg, 47% yield) was isolated as a colourless oil after purification by flash chromatography using petroleum ether :  $\text{CH}_2\text{Cl}_2$  (7 : 3) to (3 : 7).  $[\alpha]_D^{20} = -20.3$  ( $c = 1.00$ ,  $\text{CH}_3\text{OH}$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 7.83–7.79 (m, 3H), 7.70 (s, 1H), 7.48–7.42 (m, 3H), 6.04–5.89 (m, 1H), 5.21 (d,  $J = 17.2$  Hz, 1H), 5.11 (d,  $J = 10.3$  Hz, 1H), 4.68–4.62 (m, 1H), 4.53–4.44 (m,  $J = 6.8$  Hz, 1H), 3.41 (dt,  $J = 12.6, 6.2$  Hz, 1H), 2.86–2.79 (m, 1H), 2.46–2.39 (m, 1H), 1.97–1.87 (m, 1H), 1.61 (s, 3H), 1.34 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 139.7, 139.0, 133.5, 132.4, 128.2, 127.7, 127.6, 126.1, 125.8, 125.5, 125.3, 115.3, 113.5, 86.9, 85.4, 50.7, 49.6, 38.4, 27.7, 25.2. HRMS (ESI): calcd for  $\text{C}_{20}\text{H}_{23}\text{O}_2^+$  [ $\text{M} + \text{H}$ ] $^+$ , 295.1693; found, 295.1686.

**(3aS,4S,6R,6aR)-4-(3-Methoxynaphthalen-2-yl)-2,2-dimethyl-6-vinyltetrahydro-4H-cyclopenta[ $d$ ][1,3]dioxole (9g).** Following the general procedure A for iodohydrin 4 (294 mg, 1.0 mmol), the desired compound 9g (260 mg, 80% yield) was isolated as a white solid after purification by flash chromatography using petroleum ether :  $\text{CH}_2\text{Cl}_2$  (6 : 4) to (4 : 6).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 7.78 (t,  $J = 8.1$  Hz, 2H), 7.72 (s, 1H), 7.47 (t,  $J = 7.5$  Hz, 1H), 7.39 (t,  $J = 7.4$  Hz, 1H), 7.17 (s, 1H), 6.01 (ddd,  $J = 17.3, 10.2, 7.3$  Hz, 1H), 5.25 (d,  $J = 17.2$  Hz, 1H), 5.15 (d,  $J = 10.3$  Hz, 1H), 4.97 (t,  $J = 5.9$  Hz, 1H), 4.58 (t,  $J = 6.8$  Hz, 1H), 3.98 (s, 3H), 3.68 (dt,  $J = 11.7, 5.8$  Hz, 1H), 2.98–2.81 (m, 1H), 2.48–2.29 (m, 1H), 2.01 (q,  $J = 12.3$  Hz, 1H), 1.67 (s, 3H), 1.41 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 156.2, 139.3, 133.6, 132.1, 128.8, 127.6, 127.3, 126.3, 125.9, 123.8, 115.0, 112.8, 105.6, 85.7, 85.4, 55.3, 50.4, 47.0, 38.4, 28.0, 25.5. HRMS (ESI): calcd for  $\text{C}_{21}\text{H}_{25}\text{O}_3^+$  [ $\text{M} + \text{H}$ ] $^+$ , 325.1798; found, 325.1804.

**(3aS,4S,6R,6aR)-2,2-Dimethyl-4-(naphthalen-1-yl)-6-vinyl-tetrahydro-4H-cyclopenta[ $d$ ][1,3]dioxole (9h).** Following the general procedure A for iodohydrin 4 (294 mg, 1.0 mmol), the desired compound 9h (219 mg, 74% yield) was isolated as a colourless oil after purification by flash chromatography using petroleum ether :  $\text{CH}_2\text{Cl}_2$  (7 : 3) to (1 : 1).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 8.40 (d,  $J = 8.5$  Hz, 1H), 7.93 (d,  $J = 8.0$  Hz, 1H), 7.82 (d,  $J = 7.6$  Hz, 1H), 7.66–7.46 (m, 4H), 6.03 (ddd,  $J = 17.3, 10.3, 7.1$  Hz, 1H), 5.29 (d,  $J = 17.2$  Hz, 1H), 5.19 (d,  $J = 10.3$  Hz, 1H), 4.84–4.72 (m, 1H), 4.57 (t,  $J = 6.8$  Hz, 1H), 4.20–4.05 (m, 1H), 3.10–2.89 (m, 1H), 2.56–2.38 (m, 1H), 2.10 (q,  $J = 12.1$  Hz, 1H), 1.74 (s, 3H), 1.39 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 139.1, 138.4, 134.1, 132.3, 128.8, 127.3, 126.1, 125.7, 125.4, 124.2, 122.9, 115.4, 113.1, 86.7, 85.4, 49.9, 46.1, 38.2, 27.9, 25.3. HRMS (ESI): calcd for  $\text{C}_{20}\text{H}_{23}\text{O}_2^+$  [ $\text{M} + \text{H}$ ] $^+$ , 295.1693; found, 295.1694.

**(3aS,4S,6R,6aR)-4-(2,4-Difluoro-5-methylphenyl)-2,2-dimethyl-6-vinyltetrahydro-4H-cyclopenta[ $d$ ][1,3]dioxole (9i).**

Following the general procedure A for iodohydrin 4 (220 mg, 0.75 mmol), the desired compound 9i (98 mg, 45% yield, 64% yield brsm) was isolated as a colourless oil after purification by flash chromatography using petroleum ether :  $\text{CH}_2\text{Cl}_2$  (8 : 2) to (6 : 4).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 7.05 (t,  $J = 8.4$  Hz, 1H), 6.76 (t,  $J = 10.0$  Hz, 1H), 5.93 (ddd,  $J = 17.3, 10.3, 7.1$  Hz, 1H), 5.18 (d,  $J = 17.2$  Hz, 1H), 5.10 (d,  $J = 10.3$  Hz, 1H), 4.69 (t,  $J = 6.5$  Hz, 1H), 4.47 (t,  $J = 6.8$  Hz, 1H), 3.33 (dt,  $J = 12.5, 6.3$  Hz, 1H), 2.78 (dq,  $J = 13.0, 6.6$  Hz, 1H), 2.35–2.17 (m, 4H), 1.83 (q,  $J = 12.6$  Hz, 1H), 1.58 (s, 3H), 1.33 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 160.6 (dd,  $J = 60.9, 11.8$  Hz), 158.2 (dd,  $J = 60.4, 11.8$  Hz), 138.7, 130.9 (t,  $J = 6.4$  Hz), 124.2 (dd,  $J = 14.1, 4.1$  Hz), 120.4 (dd,  $J = 17.1, 3.9$  Hz), 115.3, 113.3, 103.6 (t,  $J = 26.3$  Hz), 85.6 (d,  $J = 1.3$  Hz), 85.2, 49.7, 45.3, 38.2 (d,  $J = 2.2$  Hz), 27.7, 25.2, 13.9 (d,  $J = 3.0$  Hz).  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: –116.16 to –116.38 (m), –117.60 (dd,  $J = 16.9, 8.4$  Hz). HRMS (ESI): calcd for  $\text{C}_{17}\text{H}_{21}\text{F}_2\text{O}_2^+$  [ $\text{M} + \text{H}$ ] $^+$ , 295.1504; found, 295.1505.

**3-((3aS,4S,6R,6aR)-2,2-Dimethyl-6-vinyltetrahydro-4H-cyclopenta[ $d$ ][1,3]dioxol-4-yl)pyridine (9j).** Following the general procedure A for iodohydrin 4 (220 mg, 0.75 mmol), the desired compound 9j (136 mg, 74% yield) was isolated as a colourless oil after purification by flash chromatography using petroleum ether : AcOEt :  $\text{Et}_3\text{N}$  (9 : 1 : 0.1) to (8 : 2 : 0.1).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 8.66–8.38 (m, 2H), 7.58 (d,  $J = 7.8$  Hz, 1H), 7.31–7.12 (m, 1H), 5.91 (ddd,  $J = 17.3, 10.2, 7.1$  Hz, 1H), 5.13 (dd,  $J = 33.0, 13.8$  Hz, 2H), 4.53 (t,  $J = 6.9$  Hz, 1H), 4.44 (t,  $J = 6.7$  Hz, 1H), 3.22 (dt,  $J = 12.7, 6.3$  Hz, 1H), 2.89–2.70 (m, 1H), 2.45–2.25 (m, 1H), 1.77 (q,  $J = 12.7$  Hz, 1H), 1.56 (s, 3H), 1.31 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 148.8, 148.0, 138.5, 137.5, 134.6, 123.4, 115.4, 113.7, 86.5, 85.2, 49.3, 48.3, 38.0, 27.6, 25.1. HRMS (ESI): calcd for  $\text{C}_{15}\text{H}_{20}\text{NO}_2^+$  [ $\text{M} + \text{H}$ ] $^+$ , 246.1489; found, 246.1492.

**5-((3aS,4S,6R,6aR)-2,2-Dimethyl-6-vinyltetrahydro-4H-cyclopenta[ $d$ ][1,3]dioxol-4-yl)-2-fluoropyridine (9k).** Following the general procedure A for iodohydrin 4 (220 mg, 0.75 mmol), the desired compound 9k (78 mg, 40% yield, 64% yield brsm) was isolated as a yellow oil after purification by flash chromatography using petroleum ether : AcOEt :  $\text{Et}_3\text{N}$  (50 : 5 : 0.5).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 8.11 (s, 1H), 7.71 (td,  $J = 8.3, 1.8$  Hz, 1H), 6.89 (dd,  $J = 8.3, 2.3$  Hz, 1H), 5.92 (ddd,  $J = 17.3, 10.1, 7.2$  Hz, 1H), 5.19 (d,  $J = 17.2$  Hz, 1H), 5.11 (d,  $J = 10.3$  Hz, 1H), 4.55–4.40 (m, 2H), 3.31–3.14 (m, 1H), 2.81 (td,  $J = 12.0, 6.0$  Hz, 1H), 2.36 (dt,  $J = 12.6, 6.2$  Hz, 1H), 1.76 (q,  $J = 12.6$  Hz, 1H), 1.58 (s, 3H), 1.32 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 162.7 (d,  $J = 237.9$  Hz), 145.9 (d,  $J = 14.5$  Hz), 139.9 (d,  $J = 7.8$  Hz), 138.4, 135.2 (d,  $J = 4.5$  Hz), 115.6, 113.8, 109.2 (d,  $J = 37.5$  Hz), 86.6, 85.1, 49.2, 47.5, 37.9, 27.6, 25.1.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: –71.17. HRMS (ESI): calcd for  $\text{C}_{15}\text{H}_{19}\text{FNO}_2^+$  [ $\text{M} + \text{H}$ ] $^+$ , 264.1394; found, 264.1394.

**4-((3aS,4S,6R,6aR)-2,2-Dimethyl-6-vinyltetrahydro-4H-cyclopenta[ $d$ ][1,3]dioxol-4-yl)benzonitrile (9l).** Following the general procedure A for iodohydrin 4 (147 mg, 0.5 mmol), the desired compound 9l (31 mg, 23% yield) was isolated as a yellow oil after purification by flash chromatography using petroleum ether :  $\text{CH}_2\text{Cl}_2$  (6 : 4) to (0 : 1).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 7.63 (d,  $J = 8.3$  Hz, 2H), 7.41 (d,  $J = 8.1$  Hz, 2H), 6.01–5.84 (m, 1H), 5.24–5.10 (m, 2H), 4.50 (dt,  $J = 13.3, 7.3$  Hz, 2H), 3.29 (dt,  $J =$



= 12.7, 6.3 Hz, 1H), 2.82 (td,  $J$  = 12.5, 6.3 Hz, 1H), 2.37 (dt,  $J$  = 12.7, 6.3 Hz, 1H), 1.79 (q,  $J$  = 12.7 Hz, 1H), 1.59 (s, 3H), 1.34 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 147.9, 138.6, 132.4, 128.1, 119.0, 115.7, 113.9, 110.6, 86.6, 85.3, 50.8, 49.3, 37.9, 27.7, 25.2. HRMS (ESI): calcd for  $\text{C}_{17}\text{H}_{20}\text{NO}_2^+$  [ $\text{M} + \text{H}$ ] $^+$ , 270.1489; found, 264.1491.

**((3aR,4R,6S,6aS)-2,2-Dimethyl-6-phenyltetrahydro-4H-cyclopenta[d][1,3]dioxol-4-yl)methanol (10a).** Following the general procedure B for alkene **9a** (566 mg, 2.3 mmol), the desired compound **10a** (541 mg, 95% yield) was isolated as a colourless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 7.43–7.18 (m, 5H), 4.65–4.44 (m, 2H), 3.86–3.70 (m, 2H), 3.26 (dt,  $J$  = 12.5, 6.3 Hz, 1H), 2.48–2.23 (m, 2H), 2.06 (bs, 1H), 1.76–1.68 (m, 1H), 1.60 (s, 3H), 1.35 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 142.2, 128.5, 127.1, 126.5, 113.3, 87.2, 83.1, 64.4, 50.6, 47.6, 35.0, 27.7, 25.2. HRMS (ESI): calcd for  $\text{C}_{15}\text{H}_{20}\text{NaO}_3^+$  [ $\text{M} + \text{Na}$ ] $^+$ , 271.1305; found, 271.1306.

**((3aR,4R,6S,6aS)-6-(4-Fluorophenyl)-2,2-dimethyltetrahydro-4H-cyclopenta[d][1,3]dioxol-4-yl)methanol (10b).** Following the general procedure B for alkene **9b** (109 mg, 0.42 mmol), the desired compound **10b** (100 mg, 91% yield) was isolated as a colourless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 7.22 (dd,  $J$  = 7.7, 5.9 Hz, 2H), 6.98 (t,  $J$  = 8.5 Hz, 2H), 4.56–4.38 (m, 2H), 3.79–3.59 (m, 2H), 3.19 (dt,  $J$  = 12.8, 6.4 Hz, 1H), 2.69 (bs, 1H), 2.39–2.21 (m, 2H), 1.66 (q,  $J$  = 12.4 Hz, 1H), 1.56 (s, 3H), 1.32 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 161.6 (d,  $J$  = 244.3 Hz), 137.8 (d,  $J$  = 3.2 Hz), 128.5 (d,  $J$  = 7.8 Hz), 115.2 (d,  $J$  = 21.1 Hz), 113.3, 87.1, 83.0, 64.2, 49.9, 47.4, 35.0, 30.9, 27.7, 25.2.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: –116.81. HRMS (ESI): calcd for  $\text{C}_{15}\text{H}_{20}\text{FO}_3^+$  [ $\text{M} + \text{H}$ ] $^+$ , 267.1391; found, 267.1383.

**((3aR,4R,6S,6aS)-6-(4-Methoxyphenyl)-2,2-dimethyltetrahydro-4H-cyclopenta[d][1,3]dioxol-4-yl)methanol (9c).** Following the general procedure B for alkene **9c** (164 mg, 0.59 mmol), the desired compound **10c** (143 mg, 87% yield) was isolated as a pale yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 7.19 (d,  $J$  = 8.3 Hz, 2H), 6.85 (d,  $J$  = 8.3 Hz, 2H), 4.53–4.42 (m, 2H), 3.82–3.69 (m, 5H), 3.23–3.12 (m, 1H), 2.40–2.19 (m, 2H), 1.94 (bs, 1H), 1.72–1.53 (m, 1H), 1.56 (s, 3H), 1.32 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 158.3, 134.3, 128.0, 113.9, 113.2, 87.3, 83.1, 64.5, 55.3, 49.8, 47.6, 35.1, 27.7, 25.2. HRMS (ESI): calcd for  $\text{C}_{16}\text{H}_{22}\text{NaO}_4^+$  [ $\text{M} + \text{Na}$ ] $^+$ , 301.1410; found, 301.1413.

**((3aR,4R,6S,6aS)-2,2-Dimethyl-6-(4-(trifluoromethoxy)phenyl)tetrahydro-4H-cyclopenta[d][1,3]dioxol-4-yl)methanol (9d).** Following the general procedure B for alkene **9d** (190 mg, 0.57 mmol), the desired compound **10d** (147 mg, 79% yield) was isolated as a dark yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 7.31 (d,  $J$  = 7.7 Hz, 2H), 7.17 (d,  $J$  = 8.0 Hz, 2H), 4.59–4.44 (m, 2H), 3.86–3.69 (m, 2H), 3.24 (dt,  $J$  = 12.7, 6.2 Hz, 1H), 2.58–2.22 (m, 3H), 1.78–1.59 (m, 1H), 1.59 (s, 3H), 1.34 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 147.9 (q,  $J$  = 10.1 Hz), 140.9, 128.3, 121.0, 120.5 (q,  $J$  = 252 Hz), 113.5, 87.0, 83.0, 64.2, 50.1, 47.3, 34.8, 27.6, 25.1.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: –57.96. HRMS (ESI): calcd for  $\text{C}_{16}\text{H}_{19}\text{F}_3\text{NaO}_4^+$  [ $\text{M} + \text{Na}$ ] $^+$ , 355.1128; found, 355.1129.

**((3aR,4R,6S,6aS)-2,2-Dimethyl-6-(2-methylpyridin-3-yl)tetrahydro-4H-cyclopenta[d][1,3]dioxol-4-yl)methanol (10e).** Following the general procedure B for alkene **9e** (123 mg, 0.47

mmol), the desired compound **10e** (119 mg, 97% yield) was isolated as a dark yellow oil.  $[\alpha]_{\text{D}}^{20}$  = –35.0 ( $c$  = 4.40,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 8.28 (bs, 1H), 7.48 (d,  $J$  = 7.7 Hz, 1H), 7.13–7.01 (m, 1H), 4.55–4.46 (m, 2H), 3.75–3.69 (m, 2H), 3.45–3.36 (m, 1H), 3.12 (bs, 1H), 2.61 (s, 3H), 2.39–2.25 (m, 1H), 2.20–2.15 (m, 1H), 1.71–1.62 (m, 1H), 1.53 (s, 3H), 1.26 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 157.0, 146.5, 135.8, 133.5, 121.5, 113.2, 87.0, 82.8, 63.5, 47.5, 46.6, 35.0, 27.7, 25.2, 22.7. HRMS (ESI): calcd for  $\text{C}_{15}\text{H}_{22}\text{NO}_3^+$  [ $\text{M} + \text{H}$ ] $^+$ , 264.1594; found, 264.1596.

**((3aR,4R,6S,6aS)-2,2-Dimethyl-6-(naphthalen-2-yl)tetrahydro-4H-cyclopenta[d][1,3]dioxol-4-yl)methanol (10f).** Following the general procedure B for alkene **9f** (83 mg, 0.28 mmol), the desired compound **10f** (66 mg, 80% yield) was isolated as white solid.  $[\alpha]_{\text{D}}^{20}$  = –15.3 ( $c$  = 0.44,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 7.85–7.76 (m, 3H), 7.70 (s, 1H), 7.52–7.44 (m, 3H), 4.68–4.51 (m, 2H), 3.88–3.62 (m, 2H), 3.41 (dt,  $J$  = 12.2, 6.2 Hz, 1H), 2.47–2.34 (m, 2H), 2.04 (bs, 1H), 1.82 (q,  $J$  = 11.6 Hz, 1H), 1.62 (s, 3H), 1.36 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 139.7, 133.5, 132.4, 128.2, 127.7, 127.6, 126.0, 125.8, 125.4, 125.2, 113.4, 87.0, 83.2, 64.5, 50.7, 47.6, 34.9, 27.7, 25.2. HRMS (ESI): calcd for  $\text{C}_{19}\text{H}_{22}\text{NaO}_3^+$  [ $\text{M} + \text{Na}$ ] $^+$ , 321.1461; found, 321.1464.

**((3aR,4R,6S,6aS)-6-(3-Methoxynaphthalen-2-yl)-2,2-dimethyltetrahydro-4H-cyclopenta[d][1,3]dioxol-4-yl)methanol (10g).** Following the general procedure B for alkene **9g** (249 mg, 0.76 mmol), the desired compound **10g** (249 mg, quant) was isolated as a white foam.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 7.73 (t,  $J$  = 7.1 Hz, 2H), 7.67 (s, 1H), 7.42 (t,  $J$  = 7.5 Hz, 1H), 7.34 (t,  $J$  = 7.5 Hz, 1H), 7.14 (s, 1H), 4.96–4.86 (m, 1H), 4.68–4.52 (m, 1H), 3.96 (s, 3H), 3.84–3.71 (m, 2H), 3.62 (dt,  $J$  = 19.6, 7.0 Hz, 1H), 2.48–2.26 (m, 2H), 1.82 (dd,  $J$  = 24.1, 11.9 Hz, 1H), 1.61 (s, 3H), 1.36 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 156.2, 133.5, 132.0, 128.8, 127.3, 127.3, 126.2, 125.9, 123.7, 112.8, 105.6, 85.5, 83.7, 64.9, 55.3, 48.3, 47.0, 35.1, 27.9, 25.4. HRMS (ESI): calcd for  $\text{C}_{20}\text{H}_{24}\text{NaO}_4^+$  [ $\text{M} + \text{Na}$ ] $^+$ , 351.1567; found, 351.1569.

**((3aR,4R,6S,6aS)-2,2-Dimethyl-6-(naphthalen-1-yl)tetrahydro-4H-cyclopenta[d][1,3]dioxol-4-yl)methanol (10h).** Following the general procedure B for alkene **9h** (206 mg, 0.7 mmol), the desired compound **10h** (160 mg, 77% yield) was isolated as a colourless viscous oil.  $[\alpha]_{\text{D}}^{20}$  = –60.2 ( $c$  = 5.60,  $\text{CH}_3\text{OH}$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 8.32 (d,  $J$  = 8.4 Hz, 1H), 7.89 (d,  $J$  = 7.9 Hz, 1H), 7.77 (d,  $J$  = 6.9 Hz, 1H), 7.60–7.43 (m, 4H), 4.77 (t,  $J$  = 6.4 Hz, 1H), 4.66–4.56 (m, 1H), 4.08 (dt,  $J$  = 12.1, 6.2 Hz, 1H), 3.82–3.64 (m, 2H), 2.51 (dt,  $J$  = 17.7, 6.0 Hz, 1H), 2.47–2.34 (m, 1H), 2.13 (s, 1H), 1.98–1.85 (m, 1H), 1.68 (s, 3H), 1.36 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 138.3, 134.0, 132.3, 128.8, 127.2, 126.0, 125.6, 125.4, 124.1, 122.7, 113.0, 86.8, 83.2, 64.4, 48.0, 46.2, 35.1, 27.8, 25.2. HRMS (ESI): calcd for  $\text{C}_{19}\text{H}_{22}\text{NaO}_3^+$  [ $\text{M} + \text{Na}$ ] $^+$ , 321.1461; found, 321.1463.

**((3aR,4R,6S,6aS)-6-(2,4-Difluoro-5-methylphenyl)-2,2-dimethyltetrahydro-4H-cyclopenta[d][1,3]dioxol-4-yl)methanol (10i).** Following the general procedure B for alkene **9i** (85 mg, 0.29 mmol), the desired compound **10i** (85 mg, quant) was isolated as black solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 7.04 (t,  $J$  = 8.4 Hz, 1H), 6.73 (t,  $J$  = 10.0 Hz, 1H), 4.65 (t,  $J$  = 6.8 Hz, 1H), 4.57–4.43 (m, 1H), 3.74 (ddd,  $J$  = 17.3, 10.6, 6.3 Hz, 2H), 3.31 (dt,  $J$  = 12.9, 6.6 Hz, 1H), 2.36 (dt,  $J$  = 12.1, 6.0 Hz, 1H), 2.28–2.16 (m,





4H), 1.83 (s, 1H), 1.71 (q,  $J = 12.5$  Hz, 1H), 1.56 (s, 3H), 1.32 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 160.8 (dd,  $J = 56.6$ , 11.7 Hz), 158.3 (dd,  $J = 56.0$ , 11.7 Hz), 130.9 (t,  $J = 6.4$  Hz), 124.2 (dd,  $J = 14.1$ , 4.1 Hz), 120.5 (dd,  $J = 17.1$ , 3.9 Hz), 113.4, 103.7 (t,  $J = 26.3$  Hz), 85.9, 83.1, 64.4, 47.9, 45.5, 35.0 (d,  $J = 2.1$  Hz), 27.8, 25.4, 14.1 (d,  $J = 3.0$  Hz).  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm:  $-115.25$  to  $-116.78$  (m),  $-117.45$  to  $-118.18$  (m). HRMS (ESI): calcd for  $\text{C}_{16}\text{H}_{20}\text{F}_2\text{NaO}_3^+ [\text{M} + \text{Na}]^+$ , 321.1273; found, 321.1273.

**((3aR,4R,6S,6aS)-2,2-Dimethyl-6-(pyridin-3-yl)tetrahydro-4H-cyclopenta[d][1,3]dioxol-4-yl)methanol (10j).** Following the general procedure B for alkene **9j** (116 mg, 0.47 mmol), the desired compound **10j** (95 mg, 81% yield) was isolated as a colourless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 8.61–8.39 (m, 2H), 7.62 (d,  $J = 7.8$  Hz, 1H), 7.29–7.22 (m, 1H), 4.61–4.45 (m, 2H), 3.86–3.71 (m, 2H), 3.23 (dt,  $J = 12.8$ , 6.5 Hz, 1H), 2.52–2.23 (m, 3H), 1.81–1.68 (m, 1H), 1.58 (s, 3H), 1.33 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 148.6, 147.9, 137.6, 134.7, 123.4, 113.5, 86.7, 82.9, 63.9, 48.5, 47.4, 34.5, 27.7, 25.2. HRMS (ESI): calcd for  $\text{C}_{14}\text{H}_{20}\text{NO}_3^+ [\text{M} + \text{H}]^+$ , 250.1438; found, 250.1439.

**((3aR,4R,6S,6aS)-6-(6-Fluoropyridin-3-yl)-2,2-dimethyltetrahydro-4H-cyclopenta[d][1,3]dioxol-4-yl)methanol (10k).** Following the general procedure B for alkene **9k** (75 mg, 0.28 mmol), the desired compound **10k** (69 mg, 93% yield) was isolated as a colourless viscous oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 8.10 (s, 1H), 7.74 (td,  $J = 8.2$ , 1.9 Hz, 1H), 6.90 (dd,  $J = 8.3$ , 2.0 Hz, 1H), 4.59–4.51 (m, 1H), 4.46 (t,  $J = 7.1$  Hz, 1H), 3.77 (dt,  $J = 16.6$ , 10.5 Hz, 2H), 3.22 (dt,  $J = 12.9$ , 6.5 Hz, 1H), 2.60 (s, 1H), 2.44–2.28 (m, 2H), 1.79–1.66 (m, 1H), 1.57 (s, 3H), 1.33 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 162.7 (d,  $J = 238.3$  Hz), 145.8 (d,  $J = 14.1$  Hz), 140.1 (d,  $J = 7.7$  Hz), 135.4 (d,  $J = 4.5$  Hz), 113.7, 109.4 (d,  $J = 37.1$  Hz), 86.8, 82.9, 63.8, 47.8, 47.2, 34.5, 27.7, 25.2.  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm:  $-71.47$ . Calcd for  $\text{C}_{14}\text{H}_{19}\text{FNO}_3^+ [\text{M} + \text{H}]^+$ , 268.1271; found, 268.1340.

**4-((3aS,4S,6R,6aR)-6-(Hydroxymethyl)-2,2-dimethyltetrahydro-4H-cyclopenta[d][1,3]dioxol-4-yl)benzonitrile (10l).** Following the general procedure B for alkene **9l** (274 mg, 1.02 mmol), the desired compound **10l** (112 mg, 40% yield) was isolated as a yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 7.60 (d,  $J = 8.1$  Hz, 2H), 7.40 (d,  $J = 8.1$  Hz, 2H), 4.67–4.40 (m, 2H), 3.89–3.64 (m, 2H), 3.27 (dt,  $J = 13.0$ , 6.6 Hz, 1H), 2.44–2.22 (m, 3H), 1.81–1.65 (m, 1H), 1.58 (s, 3H), 1.33 (s, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 147.9, 132.4, 128.0, 119.0, 113.7, 110.4, 86.7, 82.9, 64.0, 50.9, 47.2, 34.4, 27.7, 25.2. HRMS (ESI): calcd for  $\text{C}_{16}\text{H}_{20}\text{NO}_3^+ [\text{M} + \text{H}]^+$ , 274.1438; found, 274.1439.

**(1S,2R,3R,5S)-3-(Hydroxymethyl)-5-phenylcyclopentane-1,2-diol (11a).** Following the general procedure C for isopropylidene **10a** (61 mg, 0.24 mmol), the desired compound **11a** (50 mg, quantitative yield) was isolated as pale yellow solid.<sup>20</sup>  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  ppm: 7.31–7.23 (m, 4H), 7.17 (dd,  $J = 6.6$ , 5.4 Hz, 1H), 4.55 (t,  $J = 5.1$  Hz, 1H), 4.48–4.33 (m, 2H), 3.78–3.64 (m, 2H), 3.37–3.48 (m, 2H), 2.96 (dd,  $J = 11.2$ , 7.7 Hz, 1H), 2.12–1.94 (m, 2H), 1.30–1.23 (m, 1H).  $^{13}\text{C}$  NMR (100 MHz, DMSO)  $\delta$  ppm: 144.5, 128.5, 127.9, 126.2, 78.7, 74.0, 63.6, 49.6, 47.3, 32.3. HRMS (ESI): calcd for  $\text{C}_{12}\text{H}_{17}\text{O}_3^+ [\text{M} + \text{H}]^+$ , 209.1172; found, 209.1176.

**(1R,2S,3S,5R)-3-(4-Fluorophenyl)-5-(hydroxymethyl)cyclopentane-1,2-diol (11b).** Following the general procedure C

for isopropylidene **10b** (100 mg, 0.37 mmol), the desired compound **11b** (54 mg, 64% yield) was isolated as white solid.  $[\alpha]_{\text{D}}^{20} = -31.3$  ( $c = 0.10$ ,  $\text{CH}_3\text{OH}$ ).  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  ppm: 7.34–7.27 (m, 2H), 7.10 (t,  $J = 8.4$  Hz, 2H), 4.57 (t,  $J = 5.1$  Hz, 1H), 4.46 (d,  $J = 6.7$  Hz, 1H), 4.40 (d,  $J = 3.8$  Hz, 1H), 3.76–3.62 (m, 2H), 3.48–3.37 (m, 2H), 2.99 (dd,  $J = 18.6$ , 8.8 Hz, 1H), 2.06–1.91 (m, 2H), 1.32–1.25 (m, 1H).  $^{13}\text{C}$  NMR (100 MHz, DMSO)  $\delta$  ppm: 161.1 (d,  $J = 241.0$  Hz), 140.5 (d,  $J = 3.0$  Hz), 129.6 (d,  $J = 7.8$  Hz), 115.1 (d,  $J = 20.8$  Hz), 78.7 (s), 73.9 (s), 63.6 (s), 48.7 (s), 47.21 (s), 32.2 (s).  $^{19}\text{F}$  NMR (376 MHz, DMSO)  $\delta$  ppm:  $-117.72$ . HRMS (ESI): calcd for  $\text{C}_{12}\text{H}_{16}\text{FO}_3^+ [\text{M} + \text{H}]^+$ , 227.1079; found, 227.1080.

**(1S,2R,3R,5S)-3-(Hydroxymethyl)-5-(4-methoxyphenyl)cyclopentane-1,2-diol (11c).** Following the general procedure C for isopropylidene **10c** (80 mg, 0.29 mmol), the desired compound **11c** (69 mg, quantitative yield) was isolated as white solid.  $[\alpha]_{\text{D}}^{20} = -44.0$  ( $c = 1.00$ ,  $\text{CH}_3\text{OH}$ ).  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  ppm: 7.18 (d,  $J = 7.6$  Hz, 2H), 6.85 (d,  $J = 7.6$  Hz, 2H), 4.54 (t,  $J = 4.8$  Hz, 1H), 4.40–4.31 (m, 2H), 3.75–3.61 (m, 5H), 3.48–3.35 (m, 2H), 2.97–2.85 (m, 1H), 2.03–1.96 (m, 2H), 1.27–1.18 (m, 1H).  $^{13}\text{C}$  NMR (100 MHz, DMSO)  $\delta$  ppm: 158.0, 136.4, 128.8, 114.0, 78.7, 73.9, 63.6, 55.5, 48.7, 47.2, 32.3. HRMS (ESI): calcd for  $\text{C}_{13}\text{H}_{19}\text{O}_4^+ [\text{M} + \text{H}]^+$ , 239.1278; found, 239.1278.

**(1S,2R,3R,5S)-3-(Hydroxymethyl)-5-(4-(trifluoromethoxy)phenyl)cyclopentane-1,2-diol (11d).** Following the general procedure C for isopropylidene **10d** (91 mg, 0.28 mmol), the desired compound **11d** (78 mg, 96% yield) was isolated as white solid.  $[\alpha]_{\text{D}}^{20} = -33.8$  ( $c = 1.00$ ,  $\text{CH}_3\text{OH}$ ).  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  ppm: 7.40 (d,  $J = 8.6$  Hz, 2H), 7.27 (d,  $J = 8.2$  Hz, 2H), 4.72–4.38 (m, 3H), 3.79–3.62 (m, 2H), 3.47–3.36 (m, 2H), 3.04 (dt,  $J = 11.4$ , 8.2 Hz, 1H), 2.14–1.94 (m, 2H), 1.35–1.26 (m, 1H).  $^{13}\text{C}$  NMR (100 MHz, DMSO)  $\delta$  ppm: 147.01 (q,  $J = 1.9$  Hz), 143.9, 129.6, 121.2, 120.6 (q,  $J = 254.0$  Hz), 78.7, 73.9, 63.6, 48.7, 47.2, 32.0.  $^{19}\text{F}$  NMR (376 MHz, DMSO)  $\delta$  ppm:  $-56.83$ . HRMS (ESI): calcd for  $\text{C}_{13}\text{H}_{16}\text{F}_3\text{O}_4^+ [\text{M} + \text{H}]^+$ , 293.0995; found, 293.0998.

**(1S,2R,3R,5S)-3-(Hydroxymethyl)-5-(2-methylpyridin-3-yl)cyclopentane-1,2-diol (11e).** Following the general procedure C for isopropylidene **10e** (69 mg, 0.26 mmol), the desired compound **11e** (21 mg, 36% yield) was isolated as pale yellow highly viscous oil.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  ppm: 8.24 (d,  $J = 4.5$  Hz, 1H), 7.64 (d,  $J = 7.8$  Hz, 1H), 7.21–7.15 (m, 1H), 4.60 (t,  $J = 4.7$  Hz, 1H), 4.48 (dd,  $J = 23.4$ , 4.7 Hz, 2H), 3.84 (dd,  $J = 13.2$ , 6.2 Hz, 1H), 3.76 (s, 1H), 3.43 (dd,  $J = 11.4$ , 5.7 Hz, 2H), 3.26 (dd,  $J = 18.3$ , 8.9 Hz, 1H), 2.51 (s, 5H), 2.08 (dt,  $J = 18.3$ , 9.5 Hz, 2H), 1.15 (dd,  $J = 18.9$ , 11.3 Hz, 1H).  $^{13}\text{C}$  NMR (100 MHz, DMSO)  $\delta$  ppm: 157.2, 146.3, 137.6, 133.7, 121.9, 78.2, 73.8, 63.5, 47.1, 44.6, 31.6, 23.0. HRMS (ESI): calcd for  $\text{C}_{12}\text{H}_{18}\text{NO}_3^+ [\text{M} + \text{H}]^+$ , 224.1281; found, 224.1282.

**(1S,2R,3R,5S)-3-(Hydroxymethyl)-5-(naphthalen-2-yl)cyclopentane-1,2-diol (11f).** Following the general procedure C for isopropylidene **10f** (39 mg, 0.13 mmol), the desired compound **11f** (24 mg, 73% yield) was isolated as white solid.  $[\alpha]_{\text{D}}^{20} = -28.4$  ( $c = 1.00$ ,  $\text{CH}_3\text{OH}$ ).  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  ppm: 7.91–7.80 (m, 3H), 7.76 (s, 1H), 7.53–7.40 (m, 3H), 4.68–4.39 (m, 3H), 3.94–3.75 (m, 2H), 3.56–3.42 (m, 2H), 3.24–3.08 (m, 1H), 2.21–1.98 (m, 2H), 1.51–1.38 (m, 1H).  $^{13}\text{C}$  NMR (100 MHz, DMSO)  $\delta$  ppm: 142.1, 133.6, 132.2, 128.0, 127.8, 126.9,





126.3, 125.9, 125.6, 78.6, 74.1, 63.6, 49.7, 47.3, 32.2. HRMS (ESI): calcd for  $C_{16}H_{19}O_3^+$   $[M + H]^+$ , 259.1329; found, 259.1331.

**(1S,2R,3R,5S)-3-(Hydroxymethyl)-5-(3-methoxynaphthalen-2-yl)cyclopentane-1,2-diol (11g).** Following the general procedure C for isopropylidene **10g** (250 mg, 0.76 mmol), the desired compound **11g** (124 mg, 57% yield) was isolated as white foam after purification by flash chromatography using  $CH_2Cl_2$ : MeOH (50 : 5) to (45 : 5).  $[\alpha]_D^{20} = -70.4$  ( $c = 1.00$ ,  $CH_3OH$ ).  $^1H$  NMR (400 MHz, MeOD)  $\delta$  ppm: 7.80–7.63 (m, 3H), 7.36 (t,  $J = 7.5$  Hz, 1H), 7.28 (t,  $J = 7.5$  Hz, 1H), 7.18 (s, 1H), 4.29 (dd,  $J = 7.5$ , 5.7 Hz, 1H), 4.02 (t,  $J = 5.0$  Hz, 1H), 3.90 (s, 3H), 3.75–3.51 (m, 3H), 2.36–2.16 (m, 2H), 1.44 (dt,  $J = 10.4$ , 8.0 Hz, 1H).  $^{13}C$  NMR (100 MHz, MeOD)  $\delta$  ppm: 156.6, 133.5, 132.8, 129.0, 126.9, 126.3, 126.0, 125.3, 123.2, 104.9, 76.3, 74.2, 63.7, 54.4, 46.7, 44.8, 31.0. HRMS (ESI): calcd for  $C_{17}H_{21}O_4^+$   $[M + H]^+$ , 289.1434; found, 289.1432.

**(1S,2R,3R,5S)-3-(Hydroxymethyl)-5-(naphthalen-1-yl)cyclopentane-1,2-diol (11h).** Following the general procedure C for isopropylidene **10h** (91 mg, 0.28 mmol), the desired compound **11h** (78 mg, 96% yield) was isolated as white solid.  $^1H$  NMR (400 MHz, MeOD)  $\delta$  ppm: 8.26 (d,  $J = 8.4$  Hz, 1H), 7.84 (d,  $J = 7.9$  Hz, 1H), 7.71 (d,  $J = 8.0$  Hz, 1H), 7.53–7.42 (m, 4H), 4.26 (dd,  $J = 7.6$ , 5.6 Hz, 1H), 4.09–3.96 (m, 2H), 3.74–3.58 (m, 2H), 2.44 (dt,  $J = 12.9$ , 8.2 Hz, 1H), 2.37–2.26 (m, 1H), 1.48–1.36 (m, 1H).  $^{13}C$  NMR (100 MHz, MeOD)  $\delta$  ppm: 139.2, 134.1, 132.7, 128.3, 126.3, 125.4, 125.3, 125.0, 123.5, 122.1, 77.2, 74.2, 63.5, 46.5, 44.1, 32.1. HRMS (ESI): calcd for  $C_{16}H_{19}O_3^+$   $[M + H]^+$ , 259.1329; found, 259.1329.

**(1R,2S,3S,5R)-3-(2,4-Difluoro-5-methylphenyl)-5-(hydroxymethyl)cyclopentane-1,2-diol (11i).** Following the general procedure C for isopropylidene **10i** (78 mg, 0.26 mmol), the desired compound **11i** (43 mg, 64% yield) was isolated as white solid.  $^1H$  NMR (400 MHz, MeOD)  $\delta$  ppm: 7.10 (t,  $J = 8.5$  Hz, 1H), 6.69 (t,  $J = 10.1$  Hz, 1H), 3.98–3.73 (m, 2H), 3.57–3.40 (m, 2H), 3.24–3.18 (m, 1H), 2.12–2.04 (m, 4H), 1.31–1.22 (m, 1H).  $^{13}C$  NMR (100 MHz, MeOD)  $\delta$  ppm: 161.5–159.1 (m), 158.2 (dd,  $J = 13.3$ , 11.9 Hz), 130.5 (t,  $J = 6.3$  Hz), 125.3 (dd,  $J = 14.4$ , 4.1 Hz), 120.0 (dd,  $J = 17.0$ , 3.9 Hz), 102.5 (t,  $J = 26.8$  Hz), 76.9, 73.7, 63.4, 46.8, 42.6, 30.9, 12.5 (d,  $J = 3.2$  Hz).  $^{19}F$  NMR (376 MHz, MeOD)  $\delta$  ppm: –118.98 to –119.60 (m), –120.00 (dd,  $J = 16.3$ , 8.6 Hz). HRMS (ESI): calcd for  $C_{13}H_{17}F_2O_3^+$   $[M + H]^+$ , 259.1140; found, 259.1138.

**(1S,2R,3R,5S)-3-(Hydroxymethyl)-5-(pyridin-3-yl)cyclopentane-1,2-diol (11j).** Following the general procedure C for isopropylidene **10j** (79 mg, 0.31 mmol), the desired compound **11j** (9 mg, 13% yield) was isolated as white solid.  $^1H$  NMR (400 MHz, MeOD)  $\delta$  ppm: 8.51 (s, 1H), 8.40 (d,  $J = 4.7$  Hz, 1H), 7.84 (d,  $J = 8.0$  Hz, 1H), 7.41 (dd,  $J = 7.8$ , 4.9 Hz, 1H), 4.04–3.86 (m, 2H), 3.66 (d,  $J = 5.3$  Hz, 2H), 3.20 (dt,  $J = 16.3$ , 7.0 Hz, 1H), 2.31–2.13 (m, 2H), 1.54–1.44 (m, 1H).  $^{13}C$  NMR (100 MHz, MeOD)  $\delta$  ppm: 148.3, 146.5, 139.5, 135.7, 123.8, 78.4, 73.9, 63.3, 46.9, 46.7, 30.9. HRMS (ESI): calcd for  $C_{11}H_{16}NO_3^+$   $[M + H]^+$ , 210.1125; found, 210.1125.

**(1R,2S,3S,5R)-3-(6-Fluoropyridin-3-yl)-5-(hydroxymethyl)cyclopentane-1,2-diol (11k).** Following the general procedure C for isopropylidene **10k** (62 mg, 0.23 mmol), the desired compound **11k** (26 mg, 50% yield) was isolated as colourless oil.

$^1H$  NMR (400 MHz, MeOD)  $\delta$  ppm: 8.13 (s, 1H), 7.93 (td,  $J = 8.2$ , 2.3 Hz, 1H), 7.02 (dd,  $J = 8.5$ , 2.1 Hz, 1H), 4.01–3.81 (m, 2H), 3.63 (d,  $J = 5.4$  Hz, 2H), 3.22–3.11 (m, 1H), 2.28–2.12 (m, 2H), 1.50–1.37 (m, 1H).  $^{13}C$  NMR (100 MHz, MeOD)  $\delta$  ppm: 162.5 (d,  $J = 237.4$  Hz), 145.9 (d,  $J = 13.4$  Hz), 140.7 (d,  $J = 7.9$  Hz), 136.8 (d,  $J = 4.4$  Hz), 108.9 (d,  $J = 36.7$  Hz), 78.4, 73.8, 63.4, 46.9, 45.9, 30.9.  $^{19}F$  NMR (376 MHz, MeOD)  $\delta$  ppm: –75.20. HRMS (ESI): calcd for  $C_{11}H_{15}FNO_3^+$   $[M + H]^+$ , 228.0958; found, 228.1030.

**4-((1S,2S,3R,4R)-2,3-Dihydroxy-4-(hydroxymethyl)cyclopentyl)benzonitrile (11l).** Following the general procedure C for isopropylidene **10l** (10 mg, 0.037 mmol), the desired compound **11l** (8 mg, quant yield) was isolated as colourless oi.  $^1H$  NMR (400 MHz, MeOD)  $\delta$  ppm: 7.68 (d,  $J = 8.2$  Hz, 2H), 7.52 (d,  $J = 8.2$  Hz, 2H), 3.99–3.87 (m, 2H), 3.70–3.60 (m, 2H), 3.28–3.16 (m, 1H), 2.27–2.12 (m, 2H), 1.52–1.43 (m, 1H).  $^{13}C$  NMR (100 MHz, MeOD)  $\delta$  ppm: 149.4, 131.8, 128.4, 118.5, 109.5, 78.4, 74.0, 63.3, 49.5, 46.9, 31.2. HRMS (ESI): calcd for  $C_{13}H_{16}NO_3^+$   $[M + H]^+$ , 234.1125; found, 234.1128.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

This work was financially supported by European funding in Region Centre-Val de Loire (FEDER EURO-FÉRI EX010351), as well as by GAVO project (MERSI-CNRS). General functioning of ICOA comes from CHemBio (FEDER-FSE 2014-2020-EX003677), Techsab (FEDER-FSE 2014-2020-EX011313), RTR Motivhealth (2019-00131403) and Labex programs SYNORG (ANR-11-LABX-0029) and IRON (ANR-11-LABX-0018-01).

## References

- 1 S. Roychoudhury, A. Das, P. Sengupta, S. Dutta, S. Roychoudhury, A. P. Choudhury, A. B. F. Ahmed, S. Bhattacharjee and P. Slama, *Int. J. Environ. Res. Public Health*, 2020, **15**, 9411.
- 2 WHO, *Report of the WHO/FAO/OIE joint consultation on emerging zoonotic diseases*, World Health Organization, 2004.
- 3 S. T. Nichol, J. Arikawa and Y. Kawaoka, *Proc. Natl. Acad. Sci. U. S. A.*, 2000, **97**, 12411–12412.
- 4 Y. K. Choi, *Exp. Mol. Med.*, 2021, **53**, 711–712.
- 5 M. E. J. Woolhouse, K. Adair and L. Brierley, *Microbiol. Spectrum*, 2013, **1**, 1.
- 6 L. Wang, Y. Wang, D. Ye and Q. Liui, *Int. J. Antimicrob. Agents*, 2020, **55**, 105948.
- 7 A. J. Bennett, T. Bushmaker, K. Cameron, A. Ondzie, F. R. Niama, H. J. Parra, J. V. Mombouli, S. H. Olson, V. J. Munster and T. L. Goldberg, *Virology*, 2019, **528**, 64–72.
- 8 R. Rosenberg, *Cell. Mol. Life Sci.*, 2015, **72**, 1115–1125.
- 9 R. Carrasco-Hernandez, R. Jacome, Y. Lopez Vidal and S. Ponce de Leon, *ILAR J.*, 2017, **58**, 343–358.
- 10 S. Duffy, L. Schackelton and E. C. Holmes, *Nat. Rev. Genet.*, 2008, **9**, 267–276.



- 11 M. Slusarczyk, M. Serpi and F. Pertusati, *Antiviral Chem. Chemother.*, 2018, **26**, 2040206618775243.
- 12 V. Roy and L. A. Agrofoglio, *Drug Discovery Today*, 2022, **27**, 1945–1953.
- 13 (a) L. A. Agrofoglio and S. R. Challand, in *Acyclic, Carbocyclic and L-Nucleosides*, Kluwer Academic Publishers, Dordrecht, 1998; (b) M. Bessières, F. Chevrier, V. Roy and L. A. Agrofoglio, *Future Med. Chem.*, 2015, **7**, 1809–1828; (c) A. Mieczkowski and L. A. Agrofoglio, in *Modified Nucleosides in Biochemistry, Biotechnology and Medicine*, P. Herdewijn, Wiley-VCH GmbH & Co. KGaA, Weinheim, 2008, pp. 393–424; (d) L. A. Agrofoglio, E. Suhas, A. Farese, R. Condom, S. R. Challand, R. A. Earl and R. Guedj, *Tetrahedron*, 1994, **50**, 10611–10670; (e) A. C. Ojeda-Porras, V. Roy and L. A. Agrofoglio, *Chem. Rec.*, 2022, **22**, e202100307.
- 14 O. Boutureira, M. I. Mathieu, Y. Diaz and S. Castillon, *Chem. Soc. Rev.*, 2013, **42**, 5056–5072.
- 15 (a) R. K. Rawal, J. Bariwal and V. Singh, *Curr. Top. Med. Chem.*, 2016, **16**, 3258–3273; (b) G. J. Yuen, S. Weller and G. E. Pakes, *Clin. Pharmacokinet.*, 2008, **47**, 351–371; (c) M. Lu, Q. B. Lu and J. F. Honek, *Bioorg. Med. Chem. Lett.*, 2017, **27**, 282–287; (d) L. S. Jeong and J. A. Lee, *Antiviral Chem. Chemother.*, 2004, **15**, 235–250.
- 16 (a) J. Štambaský, M. Hocek and P. Kočovský, *Chem. Rev.*, 2009, **109**, 6729–6764; (b) K. Temburnikar and K. L. Seley-Radtke, *Beilstein J. Org. Chem.*, 2018, **14**, 772–785.
- 17 (a) L. Wang and P. G. Schultz, *Chem. Commun.*, 2002, 1–11; (b) A. A. Henry and F. E. Romesberg, *Curr. Opin. Chem. Biol.*, 2003, **7**, 727–733; (c) E. T. Kool, J. C. Morales and K. M. Guckian, *Angew. Chem., Int. Ed.*, 2000, **39**, 990–1009; (d) E. T. Kool, *Acc. Chem. Res.*, 2002, **35**, 936–943; (e) M. Stefko, R. Pohl, B. Klepetarova and M. Hocek, *Eur. J. Org. Chem.*, 2008, 1689–1704.
- 18 P. Khirsariya, P. Pospíšil, L. Maier, M. Boudný, M. Babáš, O. Kroutil, M. Mráz, R. Vácha and K. Paruch, *J. Med. Chem.*, 2022, **65**, 5701–5723.
- 19 S. J. Boyer and J. W. Leahy, *J. Org. Chem.*, 1997, **62**, 3976–3980.
- 20 S. Mishra, F. C. T. Modicom, C. L. Dean and S. P. Fletcher, *Commun. Chem.*, 2022, **5**, 154.
- 21 B. K. Chun, G. Y. Song and C. K. Chu, *J. Org. Chem.*, 2001, **66**, 4852–4858.
- 22 L. Maier, P. Khirsariya, O. Hylse, S. K. Adla, L. Cernova, M. Poljak, S. Krajcovicova, E. Weis, S. Drapela, K. Soucek and K. Paruch, *J. Org. Chem.*, 2017, **82**, 3382–3402.
- 23 (a) T. Carell, C. Brandmayr, A. Hienzsch, M. Muller, D. Pearson, V. Reiter, I. Thoma, P. Thumbs and M. Wagner, *Angew. Chem., Int. Ed.*, 2012, **51**, 7110–7131; (b) A. Marx and K. Betz, *Chem.–Eur. J.*, 2020, **26**, 3446–3463; (c) G. T. Hwang, A. M. Leconte and F. E. Romesberg, *ChemBioChem*, 2007, **8**, 1606–1611; (d) M. Stefko, L. Slavetinska, B. Klepetarova and M. Hocek, *J. Org. Chem.*, 2011, **76**, 6619–6635.
- 24 (a) S. M. Ali, K. Ramesh and R. T. Borchardt, *Tetrahedron Lett.*, 1990, **31**, 1509–1512; (b) M. S. Wolfe, B. L. Anderson, D. R. Borcharding and R. T. Borchardt, *J. Org. Chem.*, 1990, **55**, 4712–4717.
- 25 (a) M. Yang, W. Ye and S. W. Schneller, *J. Org. Chem.*, 2004, **69**, 3993–3996; (b) C. R. Johnson and Y. F. Chen, *J. Org. Chem.*, 1991, **56**, 3344–3351.
- 26 J. M. Hammann, A. K. Steib and P. Knochel, *Org. Lett.*, 2014, **16**(24), 6500–6503.
- 27 A. Guérinot and J. Cossy, *Acc. Chem. Res.*, 2020, **53**, 1351–1363.

