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Asymmetric synthesis of 6-(2′,3′,4′,5′,6′-pentafluorophenyl)-δ-lactones via ''allyl''boranes: application for the synthesis of fluorinated analog of key pharmacophore of statin drugs

P. Veeraraghavan Ramachandran*, Kamlesh J. Padiya, Vivek Rauniyar, M. Venkat Ram Reddy, Herbert C. Brown

Department of Chemistry, Herbert. C. Brown Center for Borane Research, Purdue University, 560 Oval Drive, West Lafayette, IN 47907-2084, USA

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Abstract

Asymmetric ''allyl''boration of pentafluorobenzaldehyde with various α-pinene based ''allyl''boranes provides homoallylic alcohols in high de and ee; the alcohols have been converted into δ-lactones via acryloylation, ring-closing metathesis and hydrogenation. Pentafluorophenyl analog of key pharmacophore of statin drugs has been synthesized using diastereoselective epoxidation and regioselective reduction as key steps.

Keywords: Pentafluorobenzaldehyde; α-Pinene; ''Allyl''boranes; Ring-closing metathesis; Hydrogenation; Epoxidation; Reduction

1. Introduction

Lactones are extremely versatile synthetic intermediates in organic synthesis [1]. The lactone moiety is an important structural component present in many biologically active natural products [2]. For the past few years, we have been developing methods for the synthesis of lactone containing natural and unnatural products [3]. Although there are several procedures available in the literature [1] for the synthesis of lactones, there have been only a few reports on the asymmetric synthesis of fluorolactones [4]. In continuation of some of our projects involving preparation of fluoroorganic molecules via organoboranes [5,6], we undertook the synthesis of fluorolactones via tandem asymmetric ''allyl''boration ring closing metathesis strategy.

2. Results and discussion

''Allyl''boration using α-pinene derived boranes typically provides high levels of diastereo- and enantioselectivities for homoallylic alcohols [7]. We chose four ''allyl''boranes *B*-allyldiisopinocampheylborane (**1a**) [8], (*B*)-(*Z*)-crotyldiisopinocampheyl borane (**1b**) [9], (*B*)-(*E*)-crotyldiisopinocampheylborane (**1c**) [9], and (*B*)-γ-2-methoxy-ethoxymethoxy-allyldiisopinocampheylborane (**1d**) [3a,10] (Fig. 1) and one representative aldehyde pentafluoro-benzaldehyde, **2** for the present study. ''Allyl''boration of **2** with **1a** at −100 °C took place smoothly and the homoallylic alcohol was isolated in 89% yield and 99% ee [6b]. Similarly, crotylboration of **2** with **1b** and **1c** provided the corresponding homoallylic alcohols **3b** and **3c** in >95% de and 94 and 92% ee, respectively. The de was ascertained based on ^{1}H NMR analysis of the crude product. To determine the ee, the alcohols were derivatized as either *p*-nitrobenzoate or cinnamyl esters and analyzed using HPLC on a chiralcel OD-H column.[1] Alkoxyallylboration with **1d** furnished the homoallylic alcohol **3d** in >95% de and 95% ee. The alcohols **3a–d** were esterified with acryloyl chloride in the presence of triethyl amine to yield the corresponding acrylates **4a–d**; these acrylates were subjected to ring-closing metathesis (For recent reviews, see [11]) using Grubbs' first-generation catalyst **5** (Fig. 2). The reaction was very sluggish, and afforded very low yields of products and most of the starting material was recovered. However, the reaction of acrylates **4a–d** with Grubbs' second-generation catalyst **6** took place

* Corresponding author. Tel.: +1-765-494-5303; fax: +1-765-494-0239.
E-mail address: chandran@purdue.edu (P.V. Ramachandran).

[1] Chiralcel OD-H(TM) is a Trademark of Chiral Technologies Inc. Exton, PA.

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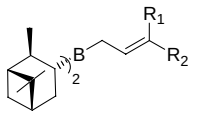
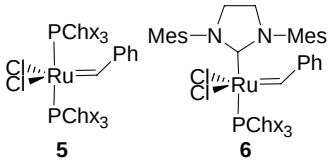


1a, R_1 = H, R_2 = H
1b, R_1 = Me, R_2 = H
1c, R_1 = H, R_2= Me
1d, R_1 = OMEM, R_2 = H

Fig. 1. Asymmetric allylborating agents.

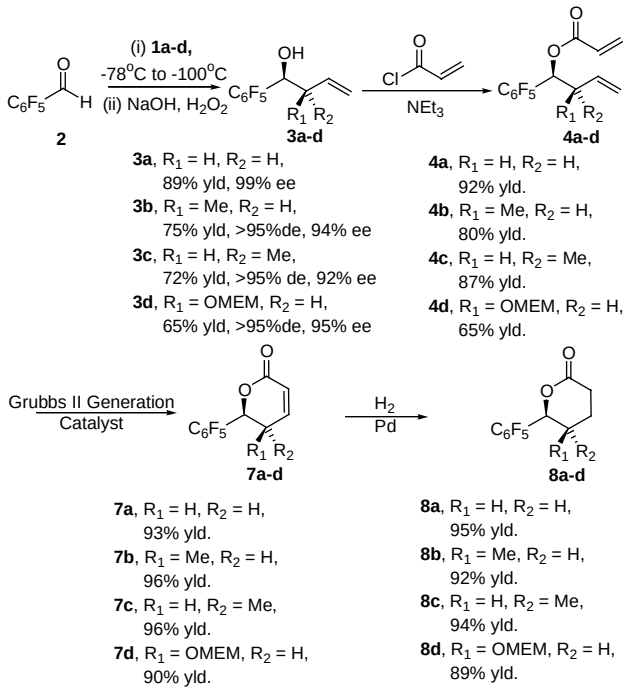


5 **6**

Fig. 2. Grubbs' catalysts for ring-closing metathesis reaction.

smoothly to afford dihydropyranones **7a–d** in excellent yields. The saturated δ-lactones **8a–d** were obtained in essentially quantitative yields upon hydrogenation of dihydropyranones **7a–d** using H_2 and Pd–C (Scheme 1).

We envisaged that the dihydropyranones **7a–d** would be useful chiral synthons for organic synthesis. To demonstrate the applicability, we undertook the synthesis of the key pharmacophore of statin drugs. Statin drugs are commercially available as prescription drugs for lowering cholesterol. Some of the blockbuster drugs[2] include Mevacor **9** [12],[3] Zocor,[4] Pravachol,[5] Lipitor **10**,[6] Lescol,[7] and the recently introduced Crestor **11** [13][8] (Fig. 3). Studies have shown that the key pharmacophore in all these drugs is the β-hydroxy-δ-lactone unit [14]. The generally beneficial effects of the fluorine substitution in a drug molecule [15] have persuaded us to prepare the fluoro-analog of the β-hydroxy-δ-lactone moiety. The dihydropyranone **7a** upon reaction with alkaline hydrogen peroxide afforded the epoxide **12** as an exlusive 1,3-*trans* isomer in 72% yield. The high diastereoselectivity obtained during the epoxidation could be explained based on the attack of the hydroperoxide ion from the face opposite to the substituent at C_5 leading to the 1,3-*trans* isomer due to the favorable stereoelectronics [16,17] (Fig. 4). The reduction of the epoxide **12** under Miyashita conditions [18] using diphenyl diselenide and sodium borohydride took place in a highly regioselective



2 **3a-d** **4a-d**

3a, R_1 = H, R_2 = H, 89% yld, 99% ee
3b, R_1 = Me, R_2 = H, 75% yld, >95%de, 94% ee
3c, R_1 = H, R_2 = Me, 72% yld, >95% de, 92% ee
3d, R_1 = OMEM, R_2 = H, 65% yld, >95%de, 95% ee

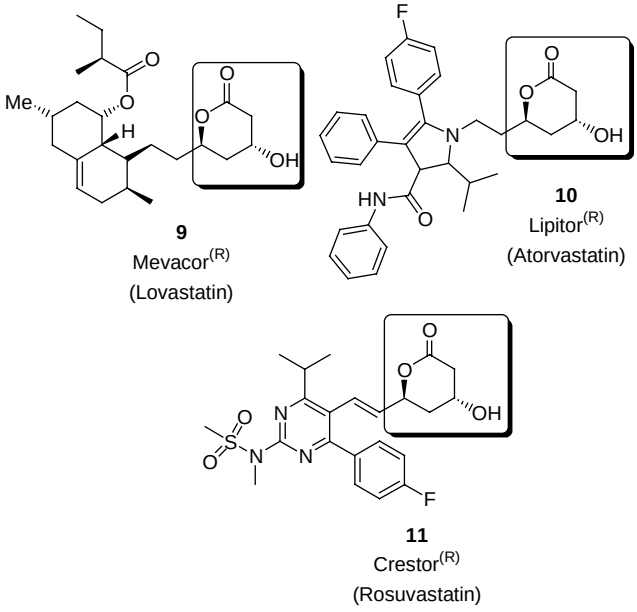
4a, R_1 = H, R_2 = H, 92% yld.
4b, R_1 = Me, R_2 = H, 80% yld.
4c, R_1 = H, R_2 = Me, 87% yld.
4d, R_1 = OMEM, R_2 = H, 65% yld.

7a-d **8a-d**

7a, R_1 = H, R_2 = H, 93% yld.
7b, R_1 = Me, R_2 = H, 96% yld.
7c, R_1 = H, R_2 = Me, 96% yld.
7d, R_1 = OMEM, R_2 = H, 90% yld.

8a, R_1 = H, R_2 = H, 95% yld.
8b, R_1 = Me, R_2 = H, 92% yld.
8c, R_1 = H, R_2 = Me, 94% yld.
8d, R_1 = OMEM, R_2 = H, 89% yld.

Scheme 1.



9 Mevacor(R) (Lovastatin)
10 Lipitor(R) (Atorvastatin)
11 Crestor(R) (Rosuvastatin)

Fig. 3. Statin drugs.

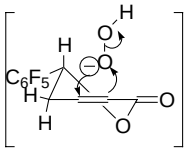
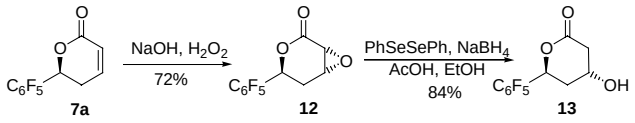


Fig. 4. Diastereomeric transition-state model for the epoxidation of pyrones.

[2] Statin drugs constituted ~6% of the total annual sale of the top 200 drugs in 1999, worth $125 billion in the USA. Lipitor, $3.0b Zocor, $2.3b Pravacol, $1.18b Mevacor, $389.5m and Lescol, $268.1m.
[3] Mevacor(r) is a trademark of Merck & Co.
[4] Launched in the market (Merck & Co.) in 1988. FDA approved new dose ranges for Zocor® in 1998.
[5] Pravachol is a trademark of Bristol–Myers Squibb. FDA approved in 1996.
[6] FDA approved in 1996, Lipitor® is a trademark of Pifizer (Parke–Davis).
[7] Lescol is a trademark of Novartis Pharma AG.
[8] Crestor® is a trademark of Astra Zenica.



Scheme 2.

manner to provide the *trans* β-hydroxy-δ-lactone **13** in 84% yield (Scheme 2).

3. Conclusions

In conlusion, we have synthesized various fluorinated α-pyrones and δ-lactones in optically pure form using α-pinene based asymmetric ''allyl''boranes. We have also synthesized a fluorinated analog of the key pharmacophore of statin drugs via diastereoselective epoxidation and regioselective reduction. Further work is in progress to synthesize fluoroanalogs of various biologically active molecules using this protocol.

4. Experimental

4.1. General experimental procedures

All operations were carried out under an inert atmosphere. The ^{1}H, ^{11}B, and ^{13}C NMR spectra were plotted on a Varian Gemini-300 spectrometer with a Nalorac-Quad probe. Mass spectra were recorded using a Hewlett-Packard 5989B mass spectrometer/5890 series II gas chromatograph or a Finnigan mass spectrometer model 4000. CI gas used was isobutane. Enantiomeric excess (% ee) was measured using Dynamax HPLC fitted with HPXL Solvent Delivery System and Dynamax UV (λ, 254 nm) detector. Chiral column used was CHIRALCEL OD-H. All the chemicals were obtained from Aldrich Chemical Company and used as received. Tetrahydrofuran was distilled from benzophenone ketyl prior to use.

4.1.1. Preparation of (1S)-1-pentafluorophenyl-3-buten-1-ol, *3a*

Aldehyde 2 (1.6 g, 8.2 mmol) was added to a stirred solution of (*B*)-allyldiisopinocampheylborane **1a** (Ipc_2BAll) (19.6 ml of 0.5 M solution in Et_2O-pentane) at −100 °C and maintained at that temperature for 2 h. The reaction was followed by ^{11}B NMR spectroscopy (δ 56). Upon completion, the mixture was oxidized with 3.6 ml of 3.0 M NaOH and 3.6 ml of 30% H_2O_2, stirred for 4 h at room temperature and extracted with Et_2O. The organic layer was dried over $MgSO_4$, concentrated under vacuum, and purified by silica gel column chromatography (hexanes: ethyl acetate, 4:1) to obtain **3a**. ^{1}H NMR: δ (ppm) ($CDCl_3$): 5.67–5.81 (m, 1H), 5.08–5.18 (m, 3H), 2.72–2.82 (m, 1H), 2.55–2.64 (m, 1H), 2.39 (bs, 1H); ^{13}C NMR: δ (ppm) ($CDCl_3$): 146.4–135.9 (m, 5C), 132.5, 119.5, 65.7, 41.2; ^{19}F NMR: δ (ppm) ($CDCl_3$) −81.15, −92.68, −99.55.

4.1.2. Preparation of (1S, 2R)-2-methyl-1-pentafluorophenyl-3-buten-1-ol, *3b*

Potassium *tert*-butoxide (5.6 ml, 1.0 M solution, 5.6 mmol) was dissolved in 10 ml THF at −78 °C and *cis*-2-butene (1.2 ml, 12.9 mmol) was added. *n*-Butyl lithium (2.3 ml, 2.5 M solution, 5.7 mmol) was added and stirred for 20 min at −45 °C. The reaction mixture was cooled to −78 °C and (−)-*B*-methoxydiisopinocampheylborane [(−)-Ipc_2BOMe] (2.2 g, 6.9 mmol) dissolved in 5.0 ml THF was added and stirred for 1 h. Aldehyde 2 (1.0 g, 5.2 mmol) was dissolved in 3.0 ml of THF, cooled to –78 °C and transferred to the reaction mixture via a canula at −78 °C and stirred for 3 h. The reaction mixture was oxidized with 2.8 ml 3 M NaOH and 2.8 ml 30% H_2O_2 and stirred overnight. The reaction mixture was worked up with ether and water. The organic layer was dried over $MgSO_4$, concentrated under vacuum and purified by column chromatography (silica gel, 5:1, hexane:ethyl ether) to obtain **3b**. ^{1}H NMR (300 MHz) δ (ppm): 5.45–5.58 (m, 1H), 4.91–5.03 (m, 2H), 4.76 (d, $J = 4.86$ Hz, 1H), 2.56–2.82 (m, 1H), 2.45 (bs, 1H), 1.12 (d, $J = 7.20$ Hz, 3H); ^{13}C NMR (75.5 MHz) δ (ppm): 138.3, 136.1–146.2 (m, 5C), 117.0, 70.5, 44.8, 16.9; ^{19}F NMR (300 MHz) δ (ppm): −80.2, −92.9, −99.8; EI–MS: *m/z* 235 $(M - OH)^+$, 197 (100%); CI–MS: *m/z* 253 $(M + H)^+$, 235 $[(M + H - H_2O)^+$, 100%].

4.1.3. Preparation of (1S, 2S)-2-methyl-1-pentafluorophenyl-3-buten-1-ol, *3c*

Procedure is same that of **3b** except that *trans*-2-butene was used instead of *cis*-2-butene. ^{1}H NMR (300 MHz) δ (ppm): 5.75–5.88 (m, 1H), 5.17–5.38 (m, 2H), 4.72 (d, $J = 4.89$ Hz, 1H), 2.56–2.82 (m, 1H), 2.42 (bs, 1H), 0.92 (d, $J = 7.17$ Hz, 3H); ^{13}C NMR (75.5 MHz) δ (ppm): 139.5, 136.0–146.6 (m, 5C), 118.1, 69.7, 44.3, 16.4; ^{19}F NMR (300 MHz) δ (ppm): −80.0, −92.8, −99.7.

4.1.4. Preparation of (1R, 2R)-2-methoxyethoxymethoxy-1-pentafluorophenyl-3-buten-1-ol, *3d*

sec-Butyl lithium (19.3 mL, 23.2 mmol) was added dropwise to a well-stirred solution of allyloxymethoxyethoxymethane (3.5 g, 24.4 mmol) in 50 ml THF at −78 °C and stirred for 0.5 h. (−) Ipc_2BOMe ((−)(*B*)-methoxydiisopinocampheylborane) (9.3 g, 29.3 mmol, 1.0 M solution in THF) was added to the reaction mixture and stirred for 1 h at −78 °C. $BF_3.Et_2O$ (5.6 ml, 44.0 mmol) was added and the reaction mixture was cooled to −100 °C. Pentafluorobenzaldehyde **2** (4.8 g, 24.4 mmol) dissolved in 10 ml THF was cooled to −78 °C and was added dropwise to the reaction mixture. It was stirred at −100 °C for 2 h and then warmed to −78 °C and stirred overnight. The reaction mixture was oxidized with 12.0 ml of 3.0 M sodium hydroxide and 12.0 ml of 30% hydrogen peroxide and stirred for 10 h at room temperature. The product was extracted with Et_2O, washed with water, and dried over $MgSO_4$. The crude

product was purified by silica gel column chromatography (hexane:ethyl acetate, 1:1) to obtain the homoallylic alcohol 3d. ^{1}H NMR (300 MHz) δ (ppm): 5.48–5.60 (m, 1H), 5.16–5.26 (m, 2H), 5.00 (d, $J = 8.31$ Hz, 1H), 4.79 (d, $J = 7.14$ Hz, 1H), 4.74 (d, $J = 7.14$ Hz, 1H), 4.51 (t, $J = 8.31$ Hz, 1H), 4.18 (bs, 1H), 3.92 (ddd, $J = 3.25$, 6.69, 11.12 Hz, 1H), 3.74 (ddd, $J = 3.03$, 4.44, 11.22 Hz, 1H), 3.58–3.61 (m, 2H), 3.42 (s, 3H); ^{13}C NMR (75.5 MHz) δ (ppm): 135.6–146.8 (m, 5C), 133.0, 120.9, 92.8, 80.1, 71.9, 68.5, 67.3, 58.8; ^{19}F NMR (300 MHz) δ (ppm): −79.4, −92.5, −100.1; EI–MS: *m/z* 235 $(M - OH)^+$, 197 (100%); CI-MS: m/z 253 $(M + H)^+$, 235 $[(M + H - H_2O)^+$, 100%].

4.1.5. Preparation of (1S)-1-pentafluorophenyl-3-butenyl prop-2-enoate, **4a**

Alcohol **3a** (0.65 g, 2.7 mmol) was dissolved in CH_2Cl_2 (6.0 ml) and cooled to 0 °C. Acryloyl chloride (0.3 ml, 4.1 mmol) and triethylamine (0.9 ml, 6.8 mmol) were added to it at 0 °C and stirred for 1 h at room temperature. After the completion of the reaction as indicated by TLC, the reaction mixture was filtered over magnesium sulphate pad and purified by column chromatography (silica gel, 9:1, hexane: ethyl acetate) to obtain pure acrylate ester **4a**. ^{1}H NMR: δ (ppm) ($CDCl_3$): 6.44 (dd, $J = 1.37$, 17.26 Hz, 1H), 6.08–6.18 (m, 2H), 5.89 (dd, $J = 1.38$, 10.44 Hz, 1H), 5.63–5.77 (m, 1H), 5.08–5.15 (m, 2H), 2.83–2.93 (m, 1H), 2.65–2.75 (m, 1H); ^{13}C NMR: δ (ppm) ($CDCl_3$): 165.0, 147.3–136.1 (m, 5C), 131.9, 131.6, 127.6, 119.4, 66.5, 37.8; ^{19}F NMR: δ (ppm) ($CDCl_3$): −79.21, −91.47, −99.32.

4.1.6. Preparation of (1S, 2S)-2-methyl-1-pentafluorophenyl-3-butenyl prop-2-enoate, **4c**

Procedure same as that of **4a**. ^{1}H NMR (300 MHz) δ (ppm): 6.43 (dd, $J = 1.47$, 17.28 Hz, 1H), 6.10 (ddd, $J = 1.50$, 11.94, 17.28 Hz, 1H), 5.73–5.90 (m, 3H), 5.08–5.17 (m, 2H), 2.86–2.99 (m, 1H), 0.96 (d, $J = 6.93$ Hz, 3H); ^{13}C NMR (75.5 MHz) δ (ppm): 165.1, 136.1–146.6 (m, 5C), 138.6, 131.8, 127.6, 116.7, 70.4, 41.4, 16.0; ^{19}F NMR (300 MHz) δ (ppm): −78.4, −91.5, −99.2.

4.1.7. Preparation of (1R, 2R)-2-(2-methoxyethoxymethoxy)-1-pentafluorophenyl-3-butenyl prop-2-enoate, **4d**

Procedure same as that of **4a**. ^{1}H NMR (300 MHz) δ (ppm): 6.47 (dd, $J = 1.26$, 17.25 Hz, 1H), 6.09–6.19 (m, 2H), 5.91 (dd, $J = 1.38$, 10.44 Hz, 1H), 5.53–5.65 (m, 1H), 5.22–5.30 (m, 2H), 4.68–4.79 (m, 3H), 3.71–3.78 (m, 1H), 3.46–3.65 (m, 3H), 3.39 (s, 3H); ^{13}C NMR (75.5 MHz) δ (ppm): 164.9, 137.8–146.8 (m, 5C), 132.2, 127.5, 121.7, 92.9, 76.7, 71.6, 68.8, 66.9, 59.0; ^{19}F NMR (300 MHz) δ (ppm): −77.6, −90.6, −99.2.

4.1.8. Preparation of (6S)-6-pentafluorophenyl-5, 6-dihydropyran-2-one, **7a**

Acrylate **4a** (0.5 g, 1.9 mmol) was heated in toluene (20.0 ml) at 80 °C. Grubbs' second-generation catalyst (0.08 g, 0.01 mmol) was added and heated for 3 h. After the completion of reaction (TLC), solvent was evaporated under vacuum and the crude product was purified by column chromatography (silica gel, 3:2, hexane:ethyl acetate) to obtain the lactenone **7a**. ^{1}H NMR: δ (ppm) ($CDCl_3$): 6.99–7.05 (m, 1H), 6.17 (dd, $J = 2.76$, 9.72 Hz, 1H), 5.79 (dd, $J = 3.83$, 12.95 Hz, 1H), 3.01–3.11 (m, 1H), 2.47–2.57 (m, 1H); ^{13}C NMR: δ (ppm) ($CDCl_3$): 162.7, 144.8, 134.2–144.4 (m, 5C), 121.4, 69.7, 28.6; ^{19}F NMR: δ (ppm) ($CDCl_3$): −78.26, −89.21, −98.28; EI–MS: *m/z* 194, 68 (100%); CI–MS: *m/z* 265 $[(M + H)^+$, 100%].

4.1.9. (5R, 6S)-5-methyl-6-pentafluorophenyl-5, 6-dihydropyran-2-one, **7b**

Procedure same as that of **7a**. ^{1}H NMR (300 MHz) δ (ppm): 7.06 (dd, $J = 6.06$, 9.90 Hz, 1H), 6.10 (d, $J = 8.85$ Hz, 1H), 5.93 (d, $J = 3.96$ Hz, 1H), 2.61–2.68 (m, 1H), 1.13 (d, $J = 7.13$ Hz, 3H); ^{13}C NMR (75.5 MHz) δ (ppm): 162.7, 150.8, 119.9, 74.5, 33.8, 12.7; EI–MS: *m/z* 195, 82 $[C_5H_6O^+$, 100%], 54; CI–MS: *m/z* 279 $[(M + H)^+$, 100%]; HRMS–CI: 279.0435 (actual), 279.0445 (calcd.).

4.1.10. (5S, 6S)-5-methyl-6-pentafluorophenyl-5, 6-dihydropyran-2-one, **7c**

Procedure same as that of **7a**. ^{1}H NMR (300 MHz) δ (ppm): 6.79 (dd, $J = 1.92$, 9.84 Hz, 1H), 6.12 (dd, $J = 2.64$, 9.81 Hz, 1H), 5.40 (d, $J = 11.79$ Hz, 1H), 3.12–3.24 (m, 1H), 1.07 (d, $J = 7.41$ Hz, 3H); ^{13}C NMR (75.5 MHz) δ (ppm): 162.6, 136.4–147.2 (m, 5C), 151.2, 120.3, 75.5, 32.7, 15.3; ^{19}F NMR (300 MHz) δ (ppm): −77.5, −88.9, −98.2; EI–MS: *m/z* 195, 82 $[C_5H_6O^+$, 100%], 54; CI–MS: *m/z* 279 $[(M + H)^+$, 100%]; HRMS–CI: 279.0435 (actual), 279.0445 (calcd.).

4.1.11. (5R, 6R)-5-(2-methoxyethoxymethoxy)-6-pentafluorophenyl-5, 6-dihydropyran-2-one, **7d**

Procedure same as that of **7a**. ^{1}H NMR (300 MHz) δ (ppm): 7.16 (dd, $J = 5.46$, 9.87 Hz, 1H), 6.27 (d, $J = 9.93$ Hz, 1H), 5.90 (d, $J = 3.51$ Hz, 1H), 4.72 (d, $J = 7.20$ Hz, 1H), 4.52 (d, $J = 7.20$ Hz, 1H), 4.26 (dd, $J = 3.60$, 5.43 Hz, 1H), 3.60–3.66 (m, 1H), 3.42–3.46 (m, 2H), 3.52 (s, 3H), 3.31–3.38 (m, 1H); ^{13}C NMR (75.5 MHz) δ (ppm): 161.4, 142.9, 123.2, 94.8, 74.1, 71.3, 67.3, 66.7, 59.0; ^{19}F NMR (75.5 MHz) δ (ppm): −76.5, −90.1, −99.0; EI–MS: *m/z* 323 (M-CH_2OCH_3), 263, 195, 89, 59 $[CH_3OCH_2CH_2^+$, 100%]; CI–MS: *m/z* 369 $[(M + H)^+$, 100%], 281, 263, 195, 172, 165, 105; HRMS–CI: 369.0753 (actual), 369.0761 (calcd).

4.1.12. Preparation of (6S)-6-pentafluorophenyl-tetrahydropyran-2-one, **8a**

Dihydro-pyranone **7a** (0.1 g, 0.5 mmol) was dissolved in ethyl acetate (2.0 ml). 0.1 g 10% palladium over charcoal was added and stirred under hydrogen atmosphere overnight. The reaction mixture was filtered over silica gel; the

crude product was concentrated under vacuum and purified by column chromatography (silica gel, hexanes:ethyl acetate, (3:1)) to obtain saturated lactone 8a. ^{1}H NMR (300 MHz) δ (ppm): 5.71 (dd, $J = 3.90$, 10.71 Hz, 1H), 2.56–2.85 (m, 2H), 1.92–2.36 (m, 4H); ^{13}C NMR (75.5 MHz) δ (ppm): 169.5, 135.6–147.5 (m, 5C), 72.7, 29.7, 27.6, 19.4; ^{19}F NMR (300 MHz) δ (ppm): −80.2, −90.2, −98.6.

4.1.13. (5R, 6S)-5-methyl-6-pentafluorophenyl tetrahydropyran-2-one, ***8b***

Procedure same as that of **8a**. ^{1}H NMR (300 MHz) δ (ppm): 5.86 (d, $J = 4.95$ Hz, 1H), 2.58–2.84 (m, 2H), 2.39–2.44 (m, 1H), 1.92–2.01 (m, 1H), 1.69–1.80 (m, 1H); 0.95 (d, $J = 6.87$ Hz, 3H); ^{13}C NMR (75.5 MHz) δ (ppm): 169.2, 134.6–146.4 (m, 5C), 77.1, 31.8, 28.8, 25.4, 14.7; ^{19}F NMR (300 MHz) δ (ppm): −77.8, −90.4, −98.5; EI–MS: *m/z* 280 $(M)^+$, 208, 181, 56 [$CH_2CH_2CO^+$, 100%]; CI–MS: *m/z* 281 [$(M + H)^+$, 100%]; HRMS–EI: *m/z* 280.0521 (actual), 280.0523 (calcd).

4.1.14. (5S, 6S)-5-Methyl-6-pentafluorophenyl tetrahydropyran-2-one, ***8c***

Procedure same as that of **8a**. ^{1}H NMR (300 MHz) δ (ppm): 5.30 (d, $J = 10.92$ Hz, 1H), 2.56–2.84 (m, 2H), 2.24–2.44 (m, 1H), 2.04–2.14 (m, 1H), 1.62–1.84 (m, 1H), 0.94 (d, $J = 6.36$ Hz, 3H); ^{13}C NMR (75.5 MHz) δ (ppm): 169.4, 136.2–146.6 (m, 5C), 78.3, 32.5, 29.9, 28.2, 16.8; ^{19}F NMR (300 MHz) δ (ppm): −79.5, −90.0, −98.6; EI–MS: *m/z* 280 $(M)^+$, 56 (100%); CI–MS: *m/z* 281 [$(M + H)^+$, 100%]; HRMS–EI: *m/z* 280.0514 (actual), 280.0523 (calcd).

4.1.15. (3R, 4R, 6S) 4-pentafluorophenyl-3, 7-dioxa-bicyclo [4.1.0] heptan-2-one, ***12***

α-Pyrone 7a (1.0 g, 3.9 mmol) in methanol was treated with 1.33 ml (13.2 mmol) of H_2O_2 and 0.39 ml of 6 N NaOH at 0 °C. The reaction mixture was stirred for 1 h, diluted with Et_2O and water, acidified with concentrated HCl, and extracted with Et_2O (3 × 50 ml). The organic layers were concentrated under aspirator vacuum. *p*PTS was added to the crude product and refluxed in toluene using a Dean–Stark apparatus. The crude product was concentrated under vacuum and purified by column chromatography (EtOAc:hexane, 1:4) to obtain the epoxy lactone **12**. ^{1}H NMR (300 MHz) δ (ppm): 5.92 (dd, $J = 3.30$, 12.30 Hz, 1H), 3.83–3.85 (m, 1H), 3.71–3.73 (m, 1H), 2.73 (dd, $J = 12.28$, 14.95 Hz, 1H), 2.53 (dt, $J = 3.12$, 14.95 Hz, 1H), ^{13}C NMR (75.5 MHz) δ (ppm): 165.9, 136.4–144.4 (m, 5C), 77.3, 65.9, 51.9, 49.0, 28.2; ^{19}F NMR (300 MHz) δ (ppm): −78.8, −88.8, −98.1.

4.1.16. (4R, 6S)-4-hydroxy-6-pentafluorophenyl-tetrahydropyran-2-one, ***13***

Sodium boro-hydride (0.057 g, 1.5 mmol) was added, in small portions, to a stirred solution of diphenyldiselenide (0.234 g, 0.75 mmol) in ethanol at RT and cooled to 0 °C. Acetic acid (0.12 ml) was then added, followed by the addition 0.14 g (0.5 mmol) of **12** dissolved in 2 ml of THF–ethanol (1:1) and stirred for 20 min. The product was extracted with ethyl acetate, washed with brine, and dried over $MgSO_4$. Evaporation of the solvents, followed by column chromatography over silica (ethyl acetate:hexane: 3:2 as eluent) provided the hydroxylactone **13**. ^{1}H NMR: δ (ppm) ($CDCl_3$): 6.15 (dd, $J = 3.83$, 11.67 Hz, 1H), 4.49–4.62 (m, 1H), 2.75–2.83 (m, 3H), 2.30–2.39 (m, 1H), 2.13–2.18 (m, 1H); ^{13}C NMR: δ (ppm) ($CDCl_3$): 169.0, 136.1–146.9 (m, 5C), 68.3, 62.7, 38.4, 34.2.

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