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Synthesis of novel bis- and oligo-*gem*-difluorocyclopropanes

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Abstract

Novel bis- and oligo-*gem*-difluorocyclopropanes have been synthesized based on the olefin metathesis reaction protocol; the ruthenium catalyst coordinated with 1,3-dimesityl-4,5-dihydroimidazol-2-ylidenc and tricyclohexylphosphine ligands gave better results than the commercial Grubbs catalyst. Syntheses of a tris-*gem*-difluorocyclopropane and three types of glycidyl-substituted difluorocyclopropanes have also been achieved.

Keywords: Fluorine compounds; Olefine metathesis; Oligo-*gem*-difluorocyclopropane; Bis-glycidyloxymethyldifluorocyclopropane

1. Introduction

The substitution of two fluorine atoms on the cyclopropane ring is expected to alter both its chemical reactivity and biological activity due to the strong electron-withdrawing nature of fluorine, and this makes it possible to create new molecules that would exhibit a unique biological activity or function (for a review, see [1–4]). The results of the optimized structure of difluorobicyclopropane (**1**) by PM3 calculation suggested a kinked form of two difluorocyclopropane groups for this compound [5]. Even more interesting, the computational chemistry suggested a highly helical shape for oligo-*gem*-difluorcyclopropanes, such as pentakis-*gem*-difluorocyclopropane (**2**), as shown in Fig. 1. Chiral-*gem*-difluorocyclopropanes are challenging targets for synthetic organic chemists [6–9]. We were attracted by the special properties of the difluorocyclopropanes and accomplished the first synthesis of optically pure 1,6-bishydroxymethyl-2,2,5,5,-tetrafluorobicycopropane (**1**) [10,11]. In the study, it was confirmed that two difluorocyclopropane groups for **1** were indeed twisted by the results of the CD spectroscopic analysis of optically active **1** in which a large CD spectral change on the Cotton's effect was observed [11]. So we undertook the synthesis of oligo-*gem*-difluorocyclopropanes through the olefin metathesis reaction protocol (for a review see [12]) and accomplished the synthesis of six types of novel bis- and oligo-*gem*-difluorocyclopropanes [13]. In this paper, we report the results of further synthetic study of novel bis- and oligo-*gem*-difluorocyclopropane.

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2. Results and discussion

First, we investigated the olefin metathesis reaction of *trans*-1-benzyloxymethyl-2,2-difluoro-3-vinylcyclopropane (**3a**) as a model compound using the Grubbs catalyst, $(PCy_3)_2Cl_2Ru$=CHPh (**5a**) [12] (Reaction (1)). We hoped that the desired coupling product **4a** would be obtained without difficulty because wide-ranging functional group tolerance has been reported for the reaction. However, compound **4a** was obtained in only poor yield (6%) in the presence of 5 mol% of the catalyst **5a**, though the stereochemistry of the newly formed olefinic part exhibited perfect (*E*)-selectivity. We tested four solvent systems: dichloromethane (CH_2Cl_2), toluene, benzene, and tetrahydrofuran (THF), and the desired product **4a** was obtained only when the reaction was carried out in CH_2Cl_2 at room temperature; significant decomposition of both substrate and the catalyst was observed at elevated temperature conditions. Increasing the amount of the catalyst caused no enhancement of the chemical yield, which remained at 5–7% even in the presence of 1.0 eq. of the catalyst, and a significant amount of unidentified purple solid was produced. We therefore used a total of 1.0 eq. of the catalyst **5a** adding 20 mol% as dichloromethane solution (0.01 M) drop-wise five times at 12 h intervals; this increased the chemical yield, and we obtained the desired coupling product **4a** in 35% yield. Recently, synthesis of a new ruthenium-based olefin metathesis catalyst **5b** which coordinated with 1,3-dimethyl-4,5-dihydroimidazol-2-ylidene ligand was reported [14,15]. Use of the catalyst **5b** gave better results than commercial catalyst **5a** and the metathesis product **4a** was obtained in the same yield even when only

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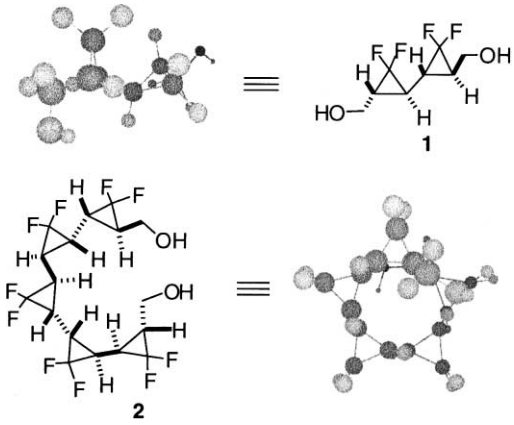
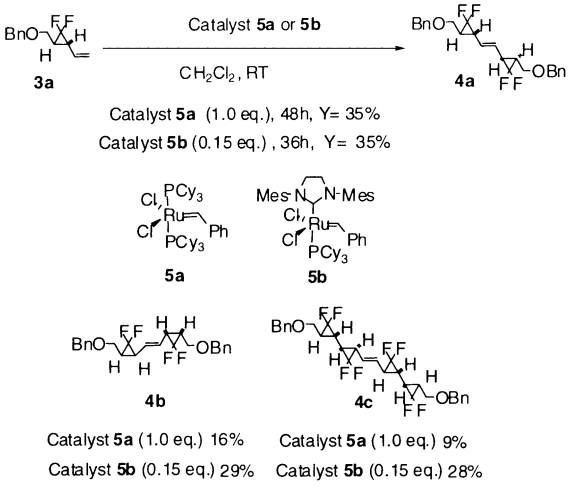


Fig. 1. Result of MO(PM3) calculation of bis- and tetrakis-*gem*-difluorocyclopropanes derivatives.

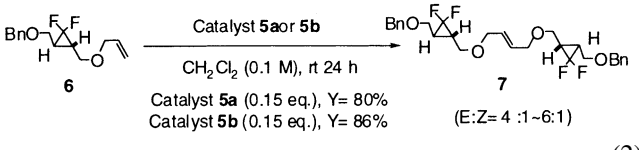
15 mol% of the catalyst was used (Reaction (1)) The drastic increase in chemical yield was recorded when bis-*gem*-difluorocyclopropane was subjected to the metathesis reaction; tetrakis-*gem*-difluorocylopropane derivative **4c** was obtained in 28% yield using this catalyst 5 h, while the chemical yield of the metathesis product was only 9% when a total of 1.0 eq. of this commercial catalyst was used following five additions of:



(1)

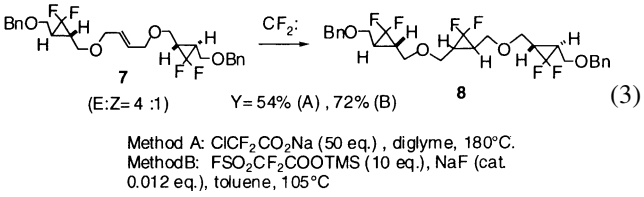
20 mol% of the catalyst **5a** at 12 h intervals.

On the other hand, the olefin metathesis reaction of allylic ether **6** proceeded successfully to give the coupling product **7** efficiently in 80% yield using 15 mol% of commercial catalyst **5a**, and the chemical yield was increased up to 86% when catalyst **5b** was employed (Reaction (2)). Stereochemistry of the newly formed olefinic part was partially controlled at the *E*:*Z* ratio of 4:1–6:1:



(2)

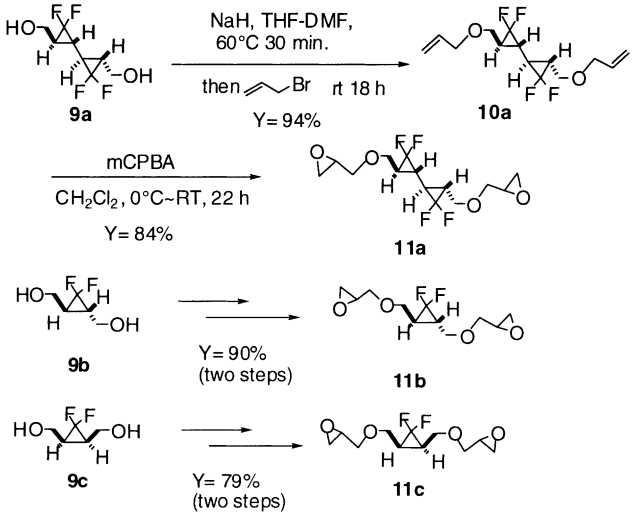
All of the products obtained, **4a**–**4c** and **7**, possess olefinic parts between the difluorocyclopropane moieties, so that we are able to add one more difluorocyclopropane group. Tris-difluorocyclopropane (*trans*,*trans*,*trans*)-**8** was synthesized in 54% yield from **7** using excess amounts of difluorocarbene (50 eq.) that was produced by the thermolysis of sodium chlorodifluoroacetate (8 M in a diglyme solution) as shown in Reaction (3) (Method A) [16]. Because this method requires excess amounts of the difluorocarbene source and a high reaction temperature, reaction using another source of difluorocarbene was investigated. Recently, a novel and efficient procedure for preparing difluorocyclopropane under milder reaction conditions using trimethylsilyl fluorosulfonyldifluoroacetate (TFDA) as the difluorocarbene source by the Dolbier and coworkers [17]; this method was applicable to our compound, and the desired tris-*gem*-difluorocyclopropane (**8**) was obtained in 72% yield using 10 eq. of the carbene source (Method B). Dolbier's procedure was, therefore, found indeed useful to prepare polydifluorocyclopropanes which possess an odd number:



(3)

of difluorocyclopropane moieties.

We applied our difluorocyclopropanes and to the synthesis of bis-glycidyl compounds (Scheme 1). Bis-allylation of *meso*-diol (**9a**) was accomplished efficiently to give **10a** in 94% yield, and subsequent epoxidation using *m*-chloroperbenzoic acid (mCPBA) afforded *meso-trans*,*trans*-1,6-bis(glycidyloxymethyl)-2,2,5,5-tetrafluorobicyclopropane (**11a**) in 84% yield. A similar compound, *trans*-1,2-bis(glycidyloxymethyl)-3,3-difluorocyclopropane (**11b**), was also



Scheme 1. Synthesis of bisglycidyloxymethyl-*gem*-difluorocyclopropanes.

obtained in 90% overall yield, while slightly reduced yield was obtained in the synthesis of *cis*-derivative (**11c**). *Cis*-difluorocyclopropanes **9c**, **10c**, and **11c** were unstable than the corresponding *trans*-isomers, especially at higher temperatures, and unidentified products formed during the reactions; this may suggest that radical ring opening of cyclopropane rings [18] of *cis*-substituted difluorocyclopropanes takes place more easily than *trans*-substituted difluorocyclopropanes. We are now synthesizing polymers that have difluorocyclopropane moieties using these bis-glycidyl compounds, hoping that a unique property might emerge from these new polymers.

3. Experimental

Reagents and solvents were purchased from common commercial sources and were used as received or purified by distillation from appropriate drying agents. Reactions requiring anhydrous conditions were run under an atmosphere of dry argon. Wako gel C-300E, was used for column chromatography and Wako gel B-5F, for thin layer chromatography. ^{1}H NMR, ^{19}F NMR, ^{13}C NMR spectra and were recorded on a Varian VXR-200 (200 MHz) spectrometer, and chemical shifts are expressed in parts per million downfield from tetramethylsilane (TMS) in $CDCl_3$ or hexafluorobenzene (C_6F_6) as internal standards. IR spectra were obtained on JASCO FT/IR-350 spectrometer.

3.1. Preparation of vinyl-substituted difluorocyclopropanes

*3.1.1. Trans-(1SR,3RS)-1-benzyloxymethyl-2,2-difluoro-3-vinylcyclopropane (**3a**)*

2-Benzyloxymethyl-3,3-difluorocylopropylmethanol (**12**) (300 mg, 1.31 mmol) was dissolved in dry CH_2Cl_2 (8.0 ml) and pyridinium dichromate (PDC) (590 mg, 1.57 mmol) was added at room temperature. After being stirred for 24 h, the mixture was filtered through a short column of Florisil (hexane/ethyl acetate = 4:1), and concentrated to give the corresponding aldehyde. This aldehyde was used immediately without further purification. A suspension of methyl triphenylphosphonium iodide (556 mg, 1.38 mmol) in dry THF (10.0 ml) was treated with *t*-BuOK (154 mg, 1.37 mmol) at 0°C and then a THF (3.0 ml) solution of the aldehyde was added to this mixture. The yellow reaction mixture was stirred at room temperature for 5 h. The crude product was purified by silica gel Hash column chromatography (hexane/ethyl acetate = 50:1) to afford **3a** (173 mg, 0.771 mmol) in 59% yield (two steps).

Rf 0.53 (hexanel/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$, *J*, Hz) δ 1.86 (1H, dddd, $J = 13.9, 13.9, 6.9, 1.6$), 2.05 (1H, dt, $J = 13.0, 7.5$), 3.46–3.73 (2H, m), 4.54 (2H, q, $J = 12.0$), 5.20 (1H, d, $J = 1.7$), 5.36 (1H, dd, $J = 29.9, 1.5$), 5.56 (1H, ddt, $J = 9.1, 3.3, 1.6$) 7.24–7.40 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$, *J*, Hz) δ 29.41 (t, $J_{C-F} = 10.0$), 30.98 (t, $J_{C-F} = 11.5$), 66.30 (d, $J_{C-F} = 47$), 72.54, 114.68 (dd, $J_{C-F} = 290.9, 288.5$), 117.92, 127.70, 127.78, 128.45, 131.19 (d, $J_{C-F} = 3.1$), 137.85; ^{19}F NMR (188 MHz, $CDCl_3$, *J*, Hz) δ 24.10 (dd, $J_{F-F} = 159.0$ $J_{H-F} = 13.2$), 25.73 (dd, $J_{F-F} = 159.0$, $J_{H-F} = 13.2$); IR (neat, cm^{-1}) 2867, 1468, 1256, 1097, 991, 740. Anal. Calcd. for $C_{13}H_{14}F_2O$: C, 69.63; H, 6.29. Found: C, 69.07; H, 6.61. The sample did not give correct elemental analysis after drying in vacuo at RT for 24 h, because this compound is unstable under distillation conditions and decomposed gradually. We used this compound for the next reaction only after chromatographic purification. Using the same procedure, *cis*-vinylcyclopropane (**3b**) and bisdifluorocyclopropane (**3c**) were also prepared from the corresponding alcohols in similar overall yield.

*3.1.2. Cis-(1SR,3SR)-1-benzyloxymethyl-2,2-difluoro-3-vinylcyclopropane (**3b**)*

Rf 0.41 (hexanel/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$, *J*, Hz) δ 2.00–2.15 (1H, m), 2.29–2.48 (1H, m), 3.58–3.66 (2H, m), 4.52 (2H, ABq, $J = 12.0$), 5.23 (1H, dd, $J = 10.3, 2.0$), 5.36 (1H, d, $J = 15.2$), 5.46–5.64 (1H, m) 7.26–7.40 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$, *J*, Hz) δ 29.40 (t, $J_{C-F} = 10.1$), 30.98 (t, $J_{C-F} = 11.1$), 65.89 (d, $J_{C-F} = 4.8$), 72.53, 114.68 (dd, $J_{C-F} = 290.9, 288.5$), 117.93, 127.70, 127.79, 128.46, 130.39 (d, $J_{C-F} = 3.6$), 137.84; ^{19}F NMR (188 MHz, $CDCl_3$, *J*, Hz) δ 24.10 (dd, $J_{F-F} = 159.0$, $J_{H-F} = 13.2$), 25.73 (dd, $J_{F-F} = 159.0$, $J_{H-F} = 13.2$); IR (neat, cm^{-1}) 2867, 1465, 1255, 1095, 990, 740. This compound was unstable under distillation conditions and decomposed completely. We used this compound for the next reaction immediately after chromatographic purification.

*3.1.3. (1SR,3RS,4RS,6SR)-1-benzyloxymethyl-2,2,5,5-tetrafluoro-6-vinylbicyclopropane (**3c**)*

Rf 0.41 (hexanel/ethyl acetate = 10:1); ^{1}H NMR (200 MHz, $CDCl_3$, *J*, Hz) δ 1.23–1.55 (2H, m), 1.83 (1H, dt, $J = 14.0, 6.9$), 2.03–2.22 (1H, m), 3.41–3.71 (2H, m), 4.53 (2H, ABq, $J = 12.0$), 5.26 (2H, d, $J = 17.7$), 5.50 (1H, dd, $J = 17.3, 8.0$), 7.15–7.40 (SH, m); ^{13}C NMR (50 MHz, $CDCl_3$, *J*, Hz) δ 23.54 (dt, $J_{C-F} = 13.0, 2.7$), 26.54 (dt, $J_{C-F} = 10.3, 4.9$), 28.20 (t, $J_{C-F} = 10.5$), 32.54 (t, $J_{C-F} = 11.2$), 66.17 (d, $J_{C-F} = 4.8$), 72.62, 113.83 (ddd, $J_{C-F} = 292.7, 288.1, 2.5$), 128.41, 128.58, 129.25, 130.52 (d, $J_{C-F} = 2.1$), 138.60; ^{19}F NMR (188 MHz, $CDCl_3$, *J*, Hz) δ 22.53 (dd, $J_{F-F} = 160.9$, $J_{H-F} = 12.2$), 24.81 (dd, $J_{F-F} = 160.7$, $J_{H-F} = 13.6$), 24.95; IR (neat, cm^{-1}) 3029, 2867, 1641, 1455, 1253, 1096, 983, 917, 784, 700. This compound was unstable under distillation conditions and decomposed completely. We used this compound for the next reaction immediately after chromatographic purification.

*3.1.4. Trans-(1SR,3SR)-1-allyloxymethyl-3-benzyloxymethyl-2,2-difluorocyclopropane (**6**)*

To a suspension of NaH (132 mg, 60% in mineral oil) in DMF (2.0 ml) was added a THF (7.5 ml) solution of 12

(502 mg, 2.20 mmol) at RT under argon atmosphere, then the mixture was stirred at 80°C for 10 min and a THF (2.5 ml) solution of allyl bromide (200 mg, 1.62 mmol) was added to this mixture. The mixture was stirred for 10 h at RT and the reaction was quenched by addition of crushed ice. The reaction mixture was extracted with ether and purified by flash chromatography on silica gel (hexane/ethyl acetate = 50:1) to give **6** (573 mg, 2.14 mmol) in 97% yield: Rf 0.58 (hexanel/ethyl acetate = 4:1); bp 180°C (1 mmHg/Kugelrohr); ^{1}H NMR (200 MHz, $CDCl_3$, *J*, Hz) δ 1.56–1.84 (2H, m), 3.45–3.69 (4H, m), 4.00 (2H, dt, $J = 5.4$, 1.4), 4.54 (2H, q, $J = 12.0$), 5.22 (1H, dt, $J = 5.9$, 1.4), 5.24 (1H, ddd, $J = 30.4$, 2.9, 1.3), 5.90 (1H, dddd, $J = 22.3$, 10.7, 5.5, 1.0) 7.25–7.48 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$, *J*, Hz) δ 26.47 (t, $J_{C-F} = 10.5$), 65.95, 71.44, 72.52, 114.80 (t, $J_{C-F} = 286.6$), 117.33, 127.68, 127.74, 128.43, 134.39, 137.89; ^{19}F NMR (188 MHz, $CDCl_3$, *J*, Hz) δ 23.53 (t, $J_{H-F} = 75$); IR (neat, cm^{-1}) 2865, 1481, 1194, 1097, 929; Anal. Calcd. for $C_{15}H_{18}F_2O_2$: C, 67.15; H, 6.76. Found: C, 66.62; H, 6.78.

3.2. Olefin metathesis reaction (Method A)

3.2.1. (E)-(1SR,3RS,6RS,8SR)-1,8-bisbenzyloxymethyl-1,3,6,8-bismethano-2,2,7,7-tetrafluorooct-4-en (**4a**)

To a solution of **3a** (22.4 mg, 0.100 mmol) in dry dichloromethane (1.0 ml) was added a solution of catalyst **5a** (16.5 mg, 0.020 mmol, 20 mol%) in dry dichloromethane (0.2 ml) at room temperature under argon atmosphere every 12 h, with stirring for 72 h. The crude product was purified by silica gel thin layer chromatography (hexane/ethyl acetate = 10:1), to afford **4a** (7.3 mg, 0.0174 mmol) in 35% yield. It was essential to use the catalyst as CH_2Cl_2 solution. No increase of the chemical yield was observed when the catalyst powder was added to the reaction mixture in a five-fold portion: Rf 0.22 (hexanel/ethyl acetate = 10:1); bp 200°C (1 mmHg/Kugelrohr); ^{1}H NMR (200 MHz, $CDCl_3$, *J*, Hz) δ 1.83 (2H, dddd, $J = 14.2$, 13.8, 7.0, 1.5), 1.94–2.12 (2H, m), 3.48–3.69 (4H, m), 4.53 (4H, ABq, $J = 11.8$), 5 39 (2H, dd, $J = 4.9$, 2.4), 7.20–7.40 (10H, m); ^{13}C NMR (50 MHz, $CDCl_3$, *J*, Hz) δ 29.86 (dt, $J_{C-F} = 19.5$, 9.9), 66.24 (d, $J = 4.8$), 72.65, 114.50 (dd, $J_{C-F} = 292.2$, 287.3), 126.57 (d, $J = 4.7$), 127.71, 127.82, 128.46, 137.76; ^{19}F NMR (188 MHz, $CDCl_3$, *J*, Hz) δ 24.08 (dd, $J = 159.0$, 13.6), 26.04 (dd, $J = 159.2$, 13.6); IR (neat, cm^{-1}) 2865, 1481, 1262, 1194, 1022, 929, 743; Anal. Calcd. for $C_{24}H_{24}F_4O_2$: C, 68.56; H, 5.75. Found: C, 68.97; H, 6.32.

3.3. Olefin metathesis reaction (Method B)

3.3.1. (E)-1,4-bis[(1RS,3SR)-3-benzyloxymethyl-2,2-difluorocyclopropylmethyl]loxybut-2-ene (**7**)

To a solution of **6** (26.8 mg, 0.100 mmol) in dry dichloromethane (1.0 ml) was added catalyst **5b** (12.7 mg, 0.015 mmol, 15 mol%) at RT under argon atmosphere, then the mixture was stirred for 24 h at RT and was quenched by saturated ammonium chloride solution, extracted with ethyl acetate, and purified by flash chromatography on silica gel (hexane/ethyl acetate = 10:1) to give **7** (21.9 mg, 0.043 mmol) in 86% yield: Rf 0.22 (hexanel/ethyl acetate = 4:1); bp 180°C (2 mmHg/Kugelrohr), mp −55 to 50°C (recrystallized from ethyl acetate); ^{1}H NMR (200 MHz, $CDCl_3$, *J*, Hz) δ 1.58–1.80 (4H, m), 3.42–3.68 (8H, m), 3.99 (4H, tt, $J = 3.0$, 1.4) (major isomer), 4.06 (4H, tt, $J = 3.1$) (minor isomer), 4.53 (4H, ABq, $J = 12.0$, 5.7), 5.71 (tt, $J = 3.6$, 1.0) (minor isomer), 5.79 (2H, tt, $J = 2.8$, 1.3) (major isomer), 7.24–7.40 (10H, m); ^{13}C NMR (50 MHz, $CDCl_3$, *J*, Hz) δ 26.43 (t, $J_{C-F} = 10.5$), 66.01, 70.30, 72.53, 114.76 (t, $J = 286.5$), 127.68, 127.75, 128.43, 129.26, 138.87; ^{19}F NMR (188 MHz, $CDCl_3$) δ 23.49 (brs); IR (neat, cm^{-1}) 2865, 1477, 1262, 1102, 743; Anal. Calcd. for $C_{28}H_{32}F_4O_4$: C, 66.13; H, 6.34. Found: C, 65.80; H, 6.36.

3.3.2. (E)-(1SR,3SR,6RS,8RS)-1,8-bisbenzyloxymethyl-1,3,6,8-bismethano-2,2,7,7-tetrafluorooct-4-en (**4b**) (major isomer)

Rf 0.29 (hexanel/ethyl acetate = 10:1); bp 200°C (1 mm Hg/Kugelrohr); ^{1}H NMR (200 MHz, $CDCl_3$, *J*, Hz) δ 1.78–2.64 (4H, m), 3.46–3.67 (4H, m), 4.43–4.58 (4H, m), 5.42 (1H, dd, $J = 11.9$, 5.0), 7.20–7.45 (10H, m); ^{13}C NMR (50 MHz, $CDCl_3$, *J*, Hz) δ 29.67 (brs), 29.88 (brs), 65.83 (d, $J_{C-F} = 4.5$) 72.65, 114.51 (dd, $J_{C-F} = 292.6$, 288.4), 127.72, 127.82, 128.46, 137.76; ^{19}F NMR (188 MHz, $CDCl_3$, *J*, Hz) δ 24.07 (2F, dd, $J = 159.0$, 13.2), 26.03 (2F, dd, $J = 159.0$, 13.2); IR (neat, cm^{-1}) 2865, 1258, 1180, 1083, 1021, 743; Anal. Calcd. for $C_{24}H_{24}F_4O_2$: C, 68.56; H, 5.75. Found: C, 68.70; H, 5.78.

3.3.3. (E)-(1SR,3RS,4RS,9SR,11RS,12RS,14SR)-1,14-bis(benzyloxymethyl)-2-3,4-6,8-9,10-11-tetra(difluoromethano)dodeca-2,4,6,8,10-tetrnene (**4c**)

Rf 0.28 (hexanel/ethyl acetate = 10:1); bp 280°C (0.8 mmHg/Kugelrohr); ^{1}H NMR (200 MHz, $CDCl_3$, *J*, Hz) δ 1.35–1.47 (2H, m), 1.74–1.92 (2H, m), 3.44–3.72 (4H, m), 4 53 (2H, ABq, $J = 11.8$), 5.27–5.43 (2H, m), 7.25–7.45 (10H, m); ^{19}F NMR (188 MHz, $CDCl_3$, *J*, Hz) δ 22.59 (dd, $J_{F-F} = 160.7$, $J_{H-F} = 10.9$), 25.03 (dd, $J_{F-F} = 162.4$, $J_{H-F} = 12.9$), 25.21 (1, $J_{H-F} = 12.9$); IR (neat, cm^{-1}) 3032, 2866, 1457, 1255, 1172, 1094, 1031, 742; Anal. Calcd. for $C_{30}H_{28}F_8O_2$: C, 62.93; H, 4.93. Found: C, 63.06; H, 4.81.

3.4. Preparation of trans-gem-difluorocyclopropane

3.4.1. Trans,trans,trans-1,2-bis[(2-benzyloxymethyl-3,3-difluoro)cyclopropylmethyl]oxy-3,3-difluorocyclopropane (**8**)

Method A (Dolbier reagent): To a mixture of **7** (50.8 mg, 0.100 mmol) and NaF (0.63 mg, 0.015 mmol) was added a toluene (0.2 ml) solution of TFDA (250.3 mg, 1.0 mmol, 10 eq.) at 120°C drop-wise over the period of 1 h by a syringe pump and the mixture was stirred for 12 h at the same temperature. After being cooled to RT, the mixture was extracted with ethyl acetate and purified by flash chromatography on silica gel (hexanel/ethyl acetate = 4:1) to give **8**

(40.2 mg, 0.072 mmol) in 72% yield. However, depending on the reaction conditions, low chemical yield was sometimes obtained.

Method B: To a diglyme (1.0 ml) solution of **7** (82.7 mg, 0.163 mmol) was added sodium chlorodifluoroacetate (1.24 g, 8.13 mmol, 50 eq.) in diglyme (9 ml) at 180°C under argon and the mixture was stirred for 7 h under reflux conditions. After being cooled to RT, the mixture was washed with iced water and extracted with a mixed solvent (hexanel/ethyl acetate = 10:1) and purified by flash chromatography on silica gel to give **8** (49 mg, 0.088 mmol) in 54% yield.

Rf 0.22 (hexanel/ethyl acetate = 4:1); bp 250°C (1 mmHg/Kugelrohr); ^{1}H NMR (200 MHz, $CDCl_3$, *J*, Hz) δ 1.56–1.80 (6H, m), 3.40–3.70 (12H, m), 4.53 (4H, ABq, $J = 11.9, 4.6$), 7.25–7.40 (10H, m); ^{13}C NMR (50 MHz, $CDCl_3$, *J*, Hz) δ 26.26 (t, $J_{C-F} = 9.3$), 26.40 (1, $J = 10.4$) 65.87, 65.97, 66.10, 66.14, 72.53, 114.70 (ddd, $J_{C-F} = 288.3$, 283.8, 2.1), 127.68, 127.76, 128.43, 137.82; ^{19}FNMR (188 MHz, $CDCl_3$, *J*, Hz) δ 23.50 (t, $J = 24.1$); IR (neat, cm^{-1}) 3033, 2870, 1480, 1372, 1264, 1194, 1103, 1019; Anal. Calcd. for $C_{29}H_{32}F_6O_4$: C, 62.36; H, 5.77. Found: C, 62.45; H, 5.97.

3.5. Preparation of bis(glycidyloxymethyl)difluorocyclopropanes

3.5.1. 1,6-Bisallyloxymethyl-2,2,5,5-tetrafluorobicyclopropane (**10a**)

To a suspension of NaH (352.5 mg, 8.81 mmol, 60% in mineral oil) in THF (3.0, 1) was added diol (**9a**) [11] (476.2 mg, 2.20 mmol) in 9.0 ml of a mixed solvent (THF and DMF = 2:1) at RT and stirred for 30 min at 60°C, then a THF (5.0 ml) solution of allyl bromide (1.09 g, 8.81 mmol) at RT and the mixture was stirred for 18 h at RT. The reaction was quenched by crashed ice and extracted with ethyl acetate. The crude product was purified by flash chromatography on silica gel (hexane/ethyl acetate = 50:1–20:1) to give **10a** (610.7 mg, 2.08 mmol) in 94% yield: Rf 0.32 (hexanel/ethyl acetate = 10:1); bp 125°C (10 mmHg/Kugelrohr); ^{1}H NMR (200 MHz, $CDCl_3$, *J*, Hz) δ 1.24–1.45 (2H, m), 1.77 (2H, dt, $J = 20.5, 6.7$), 3.45 (4H, ddd, $J = 11.0, 7.8, 1.5$), 3.88–4.09 (4H, m), 5.15–5.35 (4H, m), 5.88 (2H, ddt, $J = 17.0, 10.3$); ^{13}C NMR (50 MHz, $CDCl_3$, *J*, Hz) δ 23.38 (dt, $J_{C-F} = 11.0, 4.8$), 27.81 (t, $J_{C-F} = 9.2$), 65.64 (d, $J_{C-F} = 45$), 71.45, 112.43 (dt, $J_{C-F} = 287.3, 2.7$), 117.3, 134.3; ^{19}F NMR (188 MHz, $CDCl_3$, *J*, Hz) δ 22.52 (dd, $J = 161.4, 11.9$), 24.47 (dd, $J = 161.1, 13.6$); IR (neat, cm^{-1}) 2865, 1646, 1460, 1256, 1095, 1018, 930; Anal. Calcd. for $C_{14}H_{18}F_4O_2$: C, 57.14; H, 6.17. Found: C, 57.01; H, 6.26.

Compounds **10b** and **10c** were prepared using the same procedure.

3.5.2. Trans-(1RS,2RS)-1,2-bis(allyloxymethyl)-3,3-difluorocyclopropane (**10b**)

Rf 0.27 (hexanel/ethyl acetate = 10:1); bp 88°C (12 mmHg/Kugelrohr); ^{1}H NMR (200 MHz, $CDCl_3$, *J*, Hz) δ 1.58–1.80 (2H, m), 3.40–3.68 (4H, m), 3.87–4.11 (4H, m), 5.00–5.35 (4H, m), 5.89 (2H, ddt, $J = 17.0, 10.3, 5.6$); ^{13}C NMR (50 MHz, $CDCl_3$, *J*, Hz) δ 26.20 (t, $J_{C-F} = 10.6$), 65.85, 71.36, 114.05 (t, $J_{C-F} = 286.4$), 117.23, 134.36; ^{19}F NMR (188 MHz, $CDCl_3$, *J*, Hz) δ 23.47 (dd, $J = 8.3, 6.8$); IR (neat, cm^{-1}) 2864, 1480, 1262, 1194, 1096, 1019, 928; Anal. Calcd. for $C_{11}H_{16}F_2O_2$: C, 60.54; H, 7.39. Found: C, 59.63; H, 7.50.

3.5.3. Cis-1,2-bis(allyloxymethyl)-3,3-difluorocyclopropane (**10c**)

Rf 0.46 (hexanel/ethyl acetate = 10:1); bp 78°C (10 mmHg/Kugelrohr); ^{1}H NMR (200 MHz, $CDCl_3$, *J*, Hz) δ 1.88–2.06 (2H, m), 3.45–3.70 (4H, m), 3.87–4.10 (4H, m), 5.12–5.36 (4H, m), 5.88 (2H, ddt, $J = 17.0, 10.3, 5.7$); ^{13}C NMR (50 MHz, $CDCl_3$, *J*, Hz) δ 24.91 (t, $J_{C-F} = 10.5$), 62.92 (d, $J_{C-F} = 5.1$), 71.55, 114.16 (dd, $J_{C-F} = 289.6$, 282.9), 117.34, 134.33; ^{19}F NMR (188 MHz, $CDCl_3$, *J*, Hz) δ 10.88 (d, $J = 161.8$), 36.47 (dt, $J = 162.2, 12.3$); IR (neat, cm^{-1}) 2865, 1476, 1284, 1191, 1087, 927; Anal. Calcd. for $C_{11}H_{16}F_2O_2$: C, 60.54; H, 7.39. Found: C, 61.35; H, 7.50.

3.5.4. 1,6-Bis(2,3-epoxypropyloxymethyl)-2,2,5,5-tetrafluorobicyclopropane (**11a**)

To a CH_2Cl_2 (10 ml) solution of **10a** (235.4 mg, 0.80 mmol) was added a CH_2Cl_2 (12 ml) solution of *m*-CPBA (690.3 mg, 4.0 mmol) at 0°C and the mixture was stirred for 16 h at RT. The reaction was quenched by addition of 15 ml of the saturated aqueous solution of $Na_2S_2O_3$ and the reaction mixture was washed with saturated $NaHCO_3$ aqueous solution (15 ml) and the reaction mixture was extracted with CH_2Cl_2 and ethyl acetate. Purification of the crude product by flash chromatography on silica gel (hexane/ethyl acetate = 4:1–1:1) gave **11a** (219 mg, 0.67 mmol) in 84% yield: Rf 0.22 (hexanel/ethyl acetate = 2:1); bp 180°C (13.5 mmHg/Kugelrohr); ^{1}H NMR (200 MHz, $CDCl_3$, *J*, Hz) δ 1.22–1.45 (2H, m), 1.79 (2H, dt, $J = 20.6, 6.6$), 2.55–2.65 (2H, m), 2.75–2.83 (2H, m), 3.08–3.18 (2H, m), 3.08–3.18 (2H, m), 3.25–3.85 (8H, m); ^{13}C NMR (50 MHz, $CDCl_3$, *J*, Hz) δ 23.35 (dt, $J_{C-F} = 11.1, 4.2$), 27.67 (t, $J_{C-F} = 10.1$), 43.97, 44.03, 50.68, 67.27 (d, $J_{C-F} = 4.5$), 70.94, 71.13, 113.04 (t, $J_{C-F} = 290.1$); ^{19}F NMR (188 MHz, $CDCl_3$, *J*, Hz) δ 22.63 (dt, $J = 161.4, 10.9$), 24.45 (ddd, $J = 161.5, 22.8, 13.8$); IR (neat, cm^{-1}) 2879, 1462, 1256, 1104; Anal. Calcd. for $C_{14}H_{18}F_4O_4$: C, 51.53; H, 5.56. Found: C, 52.92; H, 5.72.

Compounds **11b** and **11c** were prepared using the same procedure.

3.5.5. Trans-(1RS,2RS)-1,2-bis(2,3-epoxypropyloxymethyl)-3,3,-difluorocyclopropane (**11b**)

Rf 0.27 (hexane/ethyl acetate = 10:1); bp 88°C (12 mmHg/Kugelrohr); ^{1}H NMR (200 MHz, $CDCl_3$, *J*, Hz) δ 1.60–1.80 (2H, m), 2.55–2.65 (2H, m), 2.78 (2H, t, $J = 4.6$), 3.10–3.20 (2H, m), 3.27–3.86 (8H, m); ^{13}C NMR

(50 MHz, $CDCl_3$, *J*, Hz) δ 26.06 (t, $J_{C-F} = 10.5$), 44.02, 50.65, 50.70, 67.02, 70.94, 71.14, 114.58; ^{19}F NMR (188 MHz, $CDCl_3$) 823.51 (brs); IR (neat, cm^{-1}) 2877, 1480, 1260, 1102; Anal. Calcd. for $C_{11}H_{16}F_2O_4$: C, 52.80; H, 6.44. Found: C, 52.94; H, 6.75.

*3.5.6. Cis-1,2-bis(2,3-epoxypropyloxymethyl)-3,3,-difluorocyclopropane (**11c**)*

Rf 0.17 (hexanel/ethyl acetate = 2:1); bp 145–148°C (12 mmHg/Kugelrohr); ^1H NMR (200 MHz, $CDCl_3$, *J*, Hz) δ 1.90–2.10 (2H, m), 2.56–2.67 (7H, m), 2.79 (2H, t, $J = 4.4$), 3.08–3.22 (2H, m), 3.26–3.45 (2H, m), 3.55–3.88 (6H, m); ^{13}C NMR (50 MHz, $CDCl_3$, *J*, Hz) δ 24.70 (t, $J_{C-F} = 10.5$), 44.06, 50.64, 50.73, 64.59 (d, $J_{C-F} = 5.1$), 71.12, 71.34, 113.97 (dd, $J_{C-F} = 289.9$, 282.8); ^{19}F NMR (188 MHz, $CDCl_3$, *J*, Hz) δ 11.12 (dt, $J = 162.1$, 15.3), 36.44 (d, $J = 161.8$); IR (neat, cm^{-1}) 2883, 1477, 1094, 1022, 906, 850; Anal. Calcd. for $C_{11}H_{16}F_2O_4$: C, 52.80; H, 6.44. Found: C, 52.69; H, 6.56.

4. Conclusion

We demonstrated the first synthesis of novel bis- and oligo-*gem*-difluorocyclopropane derivatives using olefin metathesis reaction as one of the key reactions. Using these compounds as building blocks, we can synthesize various types of novel difluorocyclopropane derivatives. We are now synthesizing hybrids of difluorocyclopropanes, amino acid, carboxylic acid, and polymeric compounds. Because the two cyclopropane rings are twisted, we are hopeful of synthesizing interesting helicaly shaped polymers using our *gem*-difluorocyclopropanes as building blocks. These studies are ongoing and we will report the results in due course.

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