# Synthesis of Both Enantiomers of $\omega$ -Trifluorononactic Acid, a New Analogue of Nonactin Monomers

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**Abstract:** Both (+)- and (-)- $\omega$ -trifluorononactic acid, a designed analogue of nonactic acid, were synthesized. The racemic acid, prepared by using *cis*-selective iodoetherification, was resolved as the corresponding (*S*)-*O*-acetylmandelates. The structure was determined by X-ray crystallographic analysis.

Key words: polynactins, antibiotics,  $\omega$ -trifluorononactic acid, chiral resolution, total synthesis

The polynactins, which include **1a-c** (Figure 1), are a series of macrotetrolide antibiotics isolated from Streptomyces strains.<sup>1</sup> Their unique structural and biological<sup>2</sup> features have led many chemists to synthesize the natural congeners 1a and 1b,<sup>3</sup> and we have reported the total synthesis of a designed polynactin analogue, macrotetrolide  $\alpha$ (1d), composed of (+)- and (-)-bishomononactic acid (2c).<sup>4</sup> Although 1d failed to exhibit either significant immunosuppressive or cytotoxic activity, bioactive analogues are still pursued. The isobutyl analogue 1e has also been reported,<sup>5</sup> but no biological studies were undertaken. As part of our ongoing studies on the chemistry of polynactins,<sup>4,6</sup> we were interested in the synthesis of nonactic acid analogues bearing a bulky substituent at the 9position, such as  $\omega$ -trifluorononactic acid (2d). A trifluoromethyl group has been found to be as large as an isopropyl or *tert*-butyl group, and makes the parent molecule more hydrophobic.<sup>7</sup> We hypothesized this curious nature of a trifluoromethyl group could confer interesting properties on the corresponding polynactin, macrotetrolide  $\beta$ (1f). Here, we describe the synthesis of both enantiomers of the monomer 2d.

A similar procedure to the synthesis of (+)- and (-)-bishomononactic acid  $(2c)^4$  was followed, that is, using *cis*selective iodoetherification and optical resolution as the key steps.

Initially, enone **4** was sought as a precursor for the iodoetherification (Scheme 1). Chain elongation of **3**<sup>4</sup> by the Horner reaction  $[(MeO)_2P(O)CH_2C(O)CF_3]$ <sup>8</sup> its enamine-type variation  $[(EtO)_2P(O)CH=C(NH_2)CF_3]$ <sup>9</sup> and the Knoevenagel reaction  $[EtOC(O)CH_2C(O)CF_3]$ <sup>10</sup> all failed to give the desired **4**, probably due to the strong electrone-

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Figure 1 Polynactin congeners and their monomers

gative effect of the trifluoromethyl group. Instead, **4** was prepared from the corresponding alcohol (*EZ*)-**5** by Wittig reaction<sup>11</sup> and oxidation. Iodoetherification<sup>12</sup> of **4**, however, did not proceed, perhaps due to the strongly electrondeficient nature of the double bond. Fortunately, iodoetherification of (*EZ*)-**5** afforded *cis*-tetrahydrofuran compound **7**. Only (*Z*)-**5** reacted under these conditions; (*E*)-**5** was completely recovered. Reductive deiodination of **7** gave a separable mixture of **8** and 8-*epi*-**8** in a ratio of 1:1. The relative configuration of the *cis*-tetrahydrofuran ring of **8** was determined by observation of an NOE correlation between 3-H and 6-H, but we could not elucidate the stereochemistry of the 8-position at this stage.

Although 8 was prepared, the overall yield was poor (4.3% from 3) and improvements to the route were sought. Next, we tried a simpler Wittig reaction (Scheme 2). Iodoetherification of Z-olefin 9 (prepared by Wittig reaction<sup>13</sup>) gave exclusively *cis*-tetrahydrofuran compound 10, which was successfully dehydroiodinated to the *E*-olefin 11, hydroboration of which<sup>14</sup> failed, probably due to steric



Scheme 1 Synthetic studies toward ( $\pm$ )-2d. *Reagents and conditions*: a) Ph<sub>3</sub>P<sup>+</sup>CH<sub>2</sub>CH(OH)CF<sub>3</sub>I<sup>-</sup>, BuLi, THF, -78 °C (37%, *E*/Z 1:1); b) Dess–Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub> (36%); c) I<sub>2</sub>, NaHCO<sub>3</sub>, MeCN; d) Bu<sub>3</sub>SnH, AIBN, toluene [each 11.5% from (*EZ*)-5].



Scheme 2 Synthetic studies toward ( $\pm$ )-2d. *Reagents and conditions*: a) Ph<sub>3</sub>P+CH<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub>I<sup>-</sup>, BuLi, Et<sub>2</sub>O, -40 to 20 °C (14%, Z only); b) I<sub>2</sub>, NaHCO<sub>3</sub>, MeCN (86%, 3,6-*cis* only); c) *t*-BuOK, DMSO (quant, *E* only); d) Ph<sub>3</sub>P+MeI<sup>-</sup>, BuLi, Et<sub>2</sub>O, -10 °C (45%); e) I<sub>2</sub>, NaHCO<sub>3</sub>, MeCN (72%, 3,6-*cis* only).

hindrance. Methylenation of **3** and iodoetherification of the resulting **12** afforded iodide **13**, however, introduction of a trifluoroacetyl group under Fukuyama coupling conditions<sup>15</sup> failed, giving the  $\beta$ -elimination product (de-*t*-Bu-**12**).

Our final plan was to use the trifluoromethyl anion as a nucleophile (Scheme 3). The counterpart electrophile **19** was prepared in five steps from **3** by Wittig reaction (to give **15**), reduction of the formyl group (to give **16**), iodo-etherification (to give **17**), deiodination (to give **18**), and oxidation. As expected, the trifluoromethyl anion obtained by treatment of trimethyl(trifluoromethyl)silane [CF<sub>3</sub>TMS] with fluoride<sup>16</sup> attacked the aldehyde **19** to give **8** and 8-*epi*-**8** was converted into **8** by oxidation (to give **14**) and reduction. In a similar manner to benzyl bishomononactate,<sup>4</sup> S<sub>N</sub>2 reactions (mesylation–oxygenation and Mitsunobu reaction) resulted in low yields.



Scheme 3 Synthetic studies toward ( $\pm$ )-2d. *Reagents and conditions*: a) Ph<sub>3</sub>P=CHCHO, toluene, 95 °C (*E* only); b) NaBH<sub>4</sub>, CeCl<sub>3</sub>·7H<sub>2</sub>O, MeOH (57% from 3); c) I<sub>2</sub>, NaHCO<sub>3</sub>, MeCN, -20 °C (79%, 3,6-*cis* only); d) Bu<sub>3</sub>SnH, AIBN, CH<sub>2</sub>Cl<sub>2</sub> (87%); e) Dess-Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; f) CF<sub>3</sub>TMS, TBAF (cat.), THF (41% for 8 and 44% for 8-*epi*-8, from 18); g) TPAP, NMO, 4 Å MS, CH<sub>2</sub>Cl<sub>2</sub>; h) NaBH<sub>4</sub>, MeOH (18%, two steps).

Optical resolution of **8** was performed as previously reported (Scheme 4).<sup>4b,c</sup> (*S*)-*O*-Acetylmandelates (+)-**20** and (+)-2,3,6,8-*epi*-**20** were easily separated by open silica gel column chromatography [ $R_f = 0.37$  for (+)-**20** and 0.42 for (+)-2,3,6,8-*epi*-**20** on silica gel TLC (hexane–EtOAc, 3:1)]. Fortunately, (+)-2,3,6,8-*epi*-**20** crystallized from hexane as colorless crystals, and X-ray crystallographic analysis (Figure 2) revealed its absolute configuration. The relative configuration of **8** and 8-*epi*-**8** was

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also clarified. Finally, hydrolysis of the two diesters afforded (+)- and (-)- $\omega$ -trifluorononactic acid (2d), respectively. These acids were purified as their benzyl esters 8.



Scheme 4 Synthesis of optically active  $\omega$ -trifluorononactic acid. *Reagents and conditions*: a) (*S*)-*O*-acetylmandelic acid, EDCI·HCl, DMAP, CH<sub>2</sub>Cl<sub>2</sub> [quant for (+)-20 and 99% for (+)-2,3,6,8-*epi*-20]; b) 1 M aq KOH, THF, MeOH; c) BnBr, *t*-BuOK, DMF [70% for (–)-8 and 92% for (+)-8].



**Figure 2** Stereochemistry of (+)-2,3,6,8-*epi*-**20** by X-ray crystallographic analysis

In conclusion, synthesis of the novel designed nonactic acid analogues, (+)- and (-)- $\omega$ -trifluorononactic acid, was achieved. The key steps were a nucleophilic addition of trifluoromethyl anion to aldehyde **19** and optical resolution of the product using (*S*)-*O*-acetylmandelic acid. Assembly of tetramer (macrotetrolide  $\beta$ ) from these nonactic acid analogues is under investigation.

Melting points were measured on a Yanako MP-J3 apparatus and are uncorrected. Optical rotation values were determined using a Horiba SEPA-300 polarimeter. FT-IR spectra were recorded as films with a Jasco 4100 spectrometer (ATR, ZnSe). <sup>1</sup>H, <sup>13</sup>C, and <sup>19</sup>F NMR spectra were recorded in CDCl<sub>3</sub> with a Varian Gemini 2000 (300 MHz for <sup>1</sup>H, 75 MHz for <sup>13</sup>C), VNMRS-600 (151 MHz for <sup>13</sup>C), or Inova 500 (470 MHz for <sup>19</sup>F) spectrometer with tetramethylsilane ( $\delta_{\rm H}$  0 ppm), CHCl<sub>3</sub> ( $\delta_{\rm C}$  77 ppm), and  $\alpha,\alpha,\alpha$ -trifluorotoluene

 $(\delta_{\rm F}$  –64 ppm) as internal standards. Mass spectra were recorded with a Jeol JMS-700 spectrometer. Merck silica gel 60 (70–230 mesh) was used for column chromatography. Merck silica gel 60 F<sub>254</sub> (0.50-mm thickness) was used for preparative TLC.

## Benzyl (2RS,3RS,6EZ)-3-tert-Butoxy-9,9,9-trifluoro-8-hydroxy-2-methylnon-6-enoate [(EZ)-5]

A 50-mL two-necked round-bottomed flask equipped with a magnetic stirrer bar, a  $N_2$  inlet adapter, and a septum was placed under a  $N_2$  atmosphere. The flask was charged with triphenyl(3,3,3-trifluoro-2-hydroxypropyl)phosphonium iodide (806 mg, 1.65 mmol) in anhyd THF (12 mL) and cooled to -78 °C. To this solution, 1.6 M BuLi in hexane (2.1 mL, 3.4 mmol) was added and the mixture was stirred for 1 h. Reddish-yellow ylide formed and to this was added a soln of **3** (335 mg, 1.09 mmol) in THF (5 mL). The solution was warmed to r.t. and stirred for 10 h. The solvent was evaporated and the residue was chromatographed on silica gel (hexane–EtOAc, 5:1) to give (*EZ*)-**5**.

Yield: 161 mg, 0.40 mmol (37%); pale yellow oil;  $R_f = 0.41$  (hexane–EtOAc, 3:1).

IR (film): 3447 (w, OH), 2973 (s), 2930 (m), 1733 (s, C=O), 1457 (m), 1364 (m), 1266 (m), 1167 (s), 1126 (s), 1046 (m), 697 (s) cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz):  $\delta$  = 1.13 (m, 3 H, 2-Me), 1.18 (s, 9 H, *t*-Bu), 1.25–1.60 (m, 2 H), 2.00–2.30 (m, 2 H), 2.76–2.88 (m, 1 H, 2-H), 3.86–3.94 (m, 1 H, 3-H), 4.30–4.40 (m, 0.5 H, 8-H), 4.64–4.78 (m, 0.5 H, 8-H), 5.06–5.20 (m, 2 H, CH<sub>2</sub>Ph), 5.39–5.53 (m, 1 H), 5.72–5.93 (m, 1 H), 7.26–7.43 (m, 5 H, Ph).

HRMS–FAB:  $m/z [M + H]^+$  calcd for  $C_{21}H_{30}F_3O_4$ : 403.2096; found: 403.2102.

#### Benzyl (2RS,3RS,6SR,7SR)-3,6-Epoxy-9,9,9-trifluoro-8-hydroxy-7-iodo-2-methylnonanoate (7)

A 20-mL two-necked round-bottomed flask equipped with a magnetic stirrer bar, a  $N_2$  inlet adapter, and a septum was placed under a  $N_2$  atmosphere. The flask was charged with  $I_2$  (267 mg, 1.05 mmol) and NaHCO<sub>3</sub> (176 mg, 2.10 mmol) in anhyd MeCN (2 mL) and cooled to 0 °C. After the addition of (*EZ*)-**5** (84 mg, 0.21 mmol), the solution was warmed to r.t. and stirred for 7.5 h. Then, the mixture was diluted with sat. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> soln and the aqueous layer was extracted with EtOAc. The combined extract was washed with brine, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure to give a mixture of **7** and (*E*)-**5** (total 76 mg). The mixture was used in the deiodination step without further purification. Part of the mixture was purified to give **7**.

Colorless oil;  $R_f = 0.30$  (hexane–EtOAc, 3:1).

IR (film): 3480 (w, OH), 1734 (s, C=O), 1264 (m), 1170 (s), 744 (m) cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz):  $\delta$  = 1.18 (d, *J* = 6.9 Hz, 3 H, 2-Me), 1.77–2.12 (m, 4 H, 4,5-H), 2.73 (dq, *J* = 8.2, 6.9 Hz, 1 H, 2-H), 3.32 (d, *J* = 5.2 Hz, 1 H, OH), 3.73–3.83 (m, 1 H), 4.06–4.23 (m, 1 H), 4.41 (dd, *J* = 3.3, 1.9 Hz, 1 H, 7-H), 5.09–5.20 (m, 1 H, 8-H), 5.13 (d, *J* = 12.6 Hz, 1 H, CHHPh), 5.20 (d, *J* = 12.6 Hz, 1 H, CHHPh), 7.26–7.40 (m, 5 H, Ph).

MS (FAB):  $m/z = 473 [M + H]^+$ .

#### Benzyl (2RS,3RS)-3-tert-Butoxy-9,9,9-trifluoro-2-methyl-8-oxonon-6-enoate (4)

A 10-mL two-necked round-bottomed flask equipped with a magnetic stirrer bar, a  $N_2$  inlet adapter, and a septum was placed under a  $N_2$  atmosphere. The flask was charged with **5** (25 mg, 0.062 mmol) in anhyd CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and cooled to 0 °C. To this solution, Dess–Martin periodinane (102 mg, 0.24 mmol) was added and the mixture was stirred for 30 min. Then, the mixture was warmed to r.t. and stirred for 24 h. The reaction mixture was quenched with sat. aq  $Na_2S_2O_3$  soln and the aqueous layer was extracted with EtOAc. The combined extract was washed with brine, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane–EtOAc, 7:1) to give **4**. This compound is unstable.

Yield: 9.0 mg, 0.022 mmol (36%); pale yellow oil;  $R_f = 0.62$  (hexane–EtOAc, 3:1).

<sup>1</sup>H NMR (300 MHz): δ = 1.14 (d, J = 7.2 Hz, 3 H, 2-Me), 1.19 (s, 9 H, *t*-Bu), 1.3–1.8 (m, 2 H, 4-H), 2.19–2.45 (m, 2 H, 5-H), 2.82 (dq, J = 7.1, 5.7 Hz, 1 H, 2-H), 3.93 (ddd, J = 8.2, 5.5, 3.6 Hz, 1 H, 3-H), 5.09 (d, J = 12.4 Hz, 1 H, CHHPh), 5.18 (d, J = 12.4 Hz, 1 H, CHHPh), 6.35 (d, J = 15.7 Hz, 1 H, 7-H), 7.21–7.32 (m, 1 H, 6-H), 7.26–7.43 (m, 5 H, Ph).

<sup>19</sup>F NMR (470 MHz):  $\delta = -78.768$  (s).

#### Benzyl (2RS,3RS,6Z)-3-tert-Butoxy-9,9,9-trifluoro-2-methylnon-6-enoate (9)

A 10-mL two-necked round-bottomed flask equipped with a magnetic stirrer bar, a  $N_2$  inlet adapter, and a septum was placed under a  $N_2$  atmosphere. The flask was charged with triphenyl(3,3,3-tri-fluoropropyl)phosphonium iodide (97 mg, 0.22 mmol) in Et<sub>2</sub>O (2 mL) and cooled to -40 °C. To this solution was added 1.6 M BuLi in hexane (0.14 mL, 0.22 mmol) and the mixture was stirred for 50 min. A reddish-yellow ylide formed and a soln of **3** (61 mg, 0.20 mmol) in Et<sub>2</sub>O (2 mL) was added to the reaction mixture. After being stirred for 2 h, the solution was warmed to r.t. and stirred overnight. To the reaction mixture was added H<sub>2</sub>O and the solution was extracted with EtOAc. The combined extract was washed with brine, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane–EtOAc, 10:1) to give **9**.

Yield: 12 mg, 0.031 mmol (14%); pale yellow oil;  $R_f = 0.56$  (hexane–EtOAc, 3:1).

<sup>1</sup>H NMR (300 MHz):  $\delta$  = 1.12 (d, *J* = 7.2 Hz, 3 H, 2-Me), 1.18 (s, 9 H, *t*-Bu), 1.30–1.56 (m, 2 H), 1.94–2.13 (m, 2 H), 2.74–2.85 (m, 3 H), 3.87–3.93 (m, 1 H, 3-H), 5.08 (d, *J* = 12.2 Hz, 1 H, CHHPh), 5.17 (d, *J* = 12.4 Hz, 1 H, CHHPh), 5.29–5.39 (m, 1 H, 7-H), 5.61 (pseudo dt, *J* = 10.7, 7.4 Hz, 1 H, 6-H), 7.32–7.40 (m, 5 H, Ph).

HRMS (EI): m/z [M<sup>+</sup>] calcd for  $C_{21}H_{29}F_3O_3$ : 386.2069; found: 386.2066.

## Benzyl (2RS,3RS,6SR,7SR)-3,6-Epoxy-9,9,9-trifluoro-7-iodo-2-methylnonanoate (10)

A 10-mL two-necked round-bottomed flask equipped with a magnetic stirrer bar, a  $N_2$  inlet adapter, and a septum was placed under a  $N_2$  atmosphere. The flask was charged with  $I_2$  (15 mg, 0.06 mmol), NaHCO<sub>3</sub> (10 mg, 0.12 mmol) and anhyd MeCN (0.5 mL). After the suspension had been stirred for 10 min at 0 °C under  $N_2$ , a soln of **9** (8.0 mg, 0.021 mmol) in anhyd MeCN (2.0 mL) was added dropwise at 0 °C. After being stirred for 16 h, the reaction was quenched with sat. aq  $Na_2S_2O_3$  soln and brine, and the mixture was extracted with EtOAc. The combined extract was washed with brine, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane–EtOAc, 3:1) to give **10**.

Yield: 8.0 mg, 0.018 mmol (86%); pale yellow oil;  $R_f = 0.37$  (hex-ane-EtOAc, 3:1).

<sup>1</sup>H NMR (300 MHz): δ = 1.18 (d, J = 7.1 Hz, 3 H, 2-Me), 1.50–1.79 (m, 2 H), 1.94–2.15 (m, 2 H), 2.62–2.80 (m, 2 H, 8-H), 2.81–3.00 (m, 1 H, 2-H), 3.46–3.56 (m, 1 H), 4.08–4.26 (m, 2 H), 5.14 (d, J = 12 Hz, 1 H, CHHPh), 5.21 (d, J = 12 Hz, 1 H, CHHPh), 7.25–7.42 (m, 5 H, Ph).

MS (FAB):  $m/z = 457 [M + H]^+$ .

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MS (EI): *m*/*z* = 456 [M<sup>+</sup>], 428, 365 [M – Bn]<sup>+</sup>, 322, 293, 177, 165, 164, 137, 107, 91, 57.

HRMS (EI): m/z [M<sup>+</sup>] calcd for C<sub>17</sub>H<sub>20</sub>F<sub>3</sub>IO<sub>3</sub>: 456.0409; found: 456.0413.

#### Benzyl (2RS,3RS,6SR,7E)-3,6-Epoxy-9,9,9-trifluoro-2-methylnon-7-enoate (11)

A 20-mL two-necked round-bottomed flask equipped with a magnetic stirrer bar, a  $N_2$  inlet adapter, and a septum was placed under a  $N_2$  atmosphere. The flask was charged with *t*-BuOK (3 mg, 0.02 mmol) in anhyd DMSO (0.5 mL). To this solution was added **10** (11 mg, 0.024 mmol) in anhyd DMSO (1.0 mL) and the mixture was stirred for 1 h at r.t. The reaction mixture was quenched with sat. NH<sub>4</sub>Cl soln and extracted with EtOAc. The combined extract was washed with brine, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane–EtOAc, 7:1) to give **11**.

Yield: 8.0 mg, 0.024 mmol (quant); pale yellow oil;  $R_f = 0.18$  (hexane–EtOAc, 5:1).

<sup>1</sup>H NMR (300 MHz):  $\delta$  = 1.16 (d, *J* = 7.1 Hz, 3 H, 2-Me), 1.58–1.75 (m, 2 H), 2.00–2.20 (m, 2 H), 2.54–2.67 (m, 1 H, 2-H), 4.16 (dt, *J* = 7.5, 6.8 Hz, 1 H), 4.40–4.53 (m, 1 H), 5.13 (d, *J* = 12.2 Hz, 1 H, CHHPh), 5.21 (d, *J* = 12.2 Hz, 1 H, CHHPh), 5.86 (ddq, *J* = 15.6, 1.9, 6.6 Hz, 1 H, 8-H), 6.36 (ddq, *J* = 15.6, 4.4, 2.2 Hz, 1 H, 7-H), 7.25–7.42 (m, 5 H, Ph).

MS (FAB):  $m/z = 329 [M + H]^+$ .

MS (EI): *m*/*z* = 328 [M<sup>+</sup>], 300, 237 [M – Bn]<sup>+</sup>, 176, 165, 107, 91.

HRMS (EI): m/z [M<sup>+</sup>] calcd for  $C_{17}H_{19}F_3O_3$ : 328.1286; found: 328.1289.

#### Benzyl (2RS,3RS)-3-tert-Butoxy-2-methylhept-6-enoate (12)

A 10-mL two-necked round-bottomed flask equipped with a magnetic stirrer bar, a  $N_2$  inlet adapter, and a septum was placed under a  $N_2$  atmosphere. The flask was charged with methyltriphenylphosphonium iodide (89 mg, 0.22 mmol) in anhyd Et<sub>2</sub>O and cooled to -10 °C. To this was added 1.6 M BuLi in hexane (0.13 mL, 0.22 mmol) and the mixture was stirred for 15 min. Reddish-yellow ylide formed, then to this was added a soln of **3** (33 mg, 0.11 mmol) in anhyd Et<sub>2</sub>O and the mixture was stirred for 1 h. To the reaction mixture was added H<sub>2</sub>O and the aqueous layer was extracted with Et<sub>2</sub>O. The combined extract was washed with brine, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane–EtOAc, 10:1) to give **12**.

Yield: 15 mg, 0.049 mmol (45%); pale yellow oil;  $R_f = 0.74$  (hexane–EtOAc, 3:1).

<sup>1</sup>H NMR (300 MHz): δ = 1.12 (d, J = 7.2 Hz, 3 H, 2-Me), 1.19 (s, 9 H, *t*-Bu), 1.25–1.58 (m, 2 H, 4-H), 1.92–2.17 (m, 2 H, 5-H), 2.80 (dq, J = 5.2, 7.2 Hz, 1 H, 2-H), 3.92 (ddd, J = 9.1, 5.2, 3.9 Hz, 1 H, 3-H), 4.88–5.02 (m, 2 H, 7-H), 5.09 (d, J = 12.4 Hz, 1 H, CHHPh), 5.17 (d, J = 12.4 Hz, 1 H, CHHPh), 5.72 (ddt, J = 17.0, 10.4, 6.3 Hz, 1 H, 6-H), 7.25–7.42 (m, 5 H, Ph).

MS (EI): *m*/*z* = 304 [M<sup>+</sup>], 248, 220, 193, 164, 141.

HRMS (EI): m/z [M<sup>+</sup>] calcd for C<sub>19</sub>H<sub>28</sub>O<sub>3</sub>: 304.2039; found: 304.2035.

# Benzyl (2RS,3RS,6SR)-3,6-Epoxy-7-iodo-2-methylheptanoate (13)

A 10-mL two-necked round-bottomed flask equipped with a magnetic stirrer bar, a  $N_2$  inlet adapter, and a septum was placed under a  $N_2$  atmosphere. The flask was charged with  $I_2$  (38 mg, 0.15 mmol) and NaHCO<sub>3</sub> (25 mg, 0.30 mmol) in anhyd MeCN (1.0 mL). After the suspension had been stirred for 10 min at 0 °C under  $N_2$ , a soln of **12** (9.0 mg, 0.030 mmol) in anhyd MeCN (2.0 mL) was added

dropwise at 0 °C. After being stirred for 21 h, the reaction was quenched with sat. aq  $Na_2S_2O_3$  soln and brine, and the aqueous layer was extracted with EtOAc. The combined extract was washed with brine, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane–EtOAc, 3:1) to give **13**.

Yield: 8.0 mg, 0.021 mmol (72%); pale yellow oil;  $R_f = 0.35$  (hexane–EtOAc, 7:1).

<sup>1</sup>H NMR (300 MHz):  $\delta$  = 1.16 (d, *J* = 7.1 Hz, 3 H, 2-Me), 1.68–1.75 (m, 2 H), 1.93–2.16 (m, 2 H), 2.66 (dq, *J* = 8.3, 7.1 Hz, 1 H, 2-H), 3.11 (dd, *J* = 9.9, 7.4 Hz, 1 H, 7-H), 3.22 (dd, *J* = 9.9, 4.4 Hz, 1 H, 7-H), 3.94–4.06 (m, 1 H), 4.12–4.23 (pseudo q, *J* = 7.7 Hz, 1 H), 5.11–5.17 (d, *J* = 12 Hz, 1 H, CHHPh), 5.18–5.22 (d, *J* = 12 Hz, 1 H, CHHPh), 7.26–7.42 (m, 5 H, Ph).

MS (EI):  $m/z = 374 [M^+]$ , 346, 283  $[M - Bn]^+$ , 240, 211, 115, 91, 58, 43.

HRMS (EI): m/z [M<sup>+</sup>] calcd for C<sub>15</sub>H<sub>19</sub>IO<sub>3</sub>: 374.0379; found: 374.0381.

## Benzyl(2RS,3RS,6E)-3-tert-Butoxy-2-methyl-8-oxooct-6-enoate (15)

A 100-mL two-necked round-bottomed flask equipped with a magnetic stirrer bar, a reflux condenser with a  $N_2$  inlet adapter, and a septum was placed under a  $N_2$  atmosphere. The flask was charged with **3** (615 mg, 2.01 mmol) and Ph<sub>3</sub>P=CHCHO (1.04 g, 3.42 mmol) in toluene (25 mL). The mixture was stirred for 18 h at 95 °C. The solvent was evaporated and the residue was chromatographed on silica gel (hexane–EtOAc, 4:1) which gave a mixture of **15** and **3** (ca. 5.1:1.7, 539 mg). Part of the mixture was purified to give **15** as a colorless oil.

<sup>1</sup>H NMR (300 MHz):  $\delta$  = 1.14 (d, *J* = 6.9 Hz, 3 H, 2-Me), 1.19 (s, 9 H, *t*-Bu), 1.35–1.47 (m, 1 H, 4-H), 1.54–1.66 (m, 1 H, 4-H), 2.20–2.45 (m, 2 H, 5-H), 2.83 (dq, *J* = 6.9, 5.5 Hz, 1 H, 2-H), 3.90–3.97 (m, 1 H, 3-H), 5.07–5.11 (d, *J* = 12.6 Hz, 1 H, CHHPh), 5.17–5.23 (d, *J* = 12.6 Hz, 1 H, CHHPh), 6.06 (dd, *J* = 15.6, 7.7 Hz, 1 H, 7-H), 6.74 (dt, *J* = 15.6, 6.6 Hz, 1 H, 6-H), 7.24–7.41 (m, 5 H, Ph), 9.44 (d, *J* = 7.7 Hz, 1 H, 8-H).

HRMS–FAB: m/z [M + Na]<sup>+</sup> calcd for C<sub>20</sub>H<sub>28</sub>NaO<sub>4</sub>: 355.1885; found: 355.1894.

#### Benzyl (2RS,3RS,6E)-3-tert-Butoxy-8-hydroxy-2-methyloct-6enoate (16)

A 200-mL three-necked round-bottomed flask equipped with a magnetic stirrer bar, a  $N_2$  inlet adapter, and a septum was placed under a  $N_2$  atmosphere. The flask was charged with the mixture of **15** and **3** (539 mg) in MeOH (50 mL). To this solution was added CeCl<sub>3</sub>·7H<sub>2</sub>O (905 mg, 2.43 mmol) at 0 °C and the mixture was stirred for 5 min. Then, to this was added NaBH<sub>4</sub> (92 mg, 2.4 mmol) and the mixture was stirred for a further 15 min. The reaction mixture was diluted with sat. aq NH<sub>4</sub>Cl soln and concentrated under reduced pressure, and the residue was extracted with EtOAc. The combined extract was washed with brine, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane–EtOAc, 5:1) to give **16**.

Yield: 400 mg, 1.20 mmol (57%, two steps from **3**); pale yellow oil;  $R_f = 0.20$  (hexane–EtOAc, 3:1).

IR (film): 3448 (w, OH), 2974 (s), 2930 (s), 2850 (m), 1734 (s, C=O), 1457 (m), 1364 (m), 1254 (m), 1190 (m), 1050 (m), 748 (w), 698 (w) cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz): δ = 1.12 (d, J = 7.1 Hz, 3 H, 2-Me), 1.18 (s, 9 H, *t*-Bu), 1.27–1.42 (m, 1 H), 1.43–1.58 (m, 1 H), 1.92–2.16 (m, 2 H), 2.74–2.85 (quintet, J = 7.1 Hz, 1 H, 2-H), 3.87–3.94 (m, 1 H, 3-H), 4.01–4.08 (m, 2 H, 8-H), 5.06–5.12 (d, J = 12.6 Hz, 1 H,

C*H*HPh), 5.13–5.19 (d, *J* = 12.6 Hz, 1 H, CH*H*Ph), 5.58–5.63 (m, 2 H, 6,7-H), 7.27–7.40 (m, 5 H, Ph).

 $^{13}\text{C}$  NMR (75 MHz):  $\delta$  = 174.75, 136.25, 133.05, 129.14, 128.59, 128.20, 73.90, 71.61, 66.00, 63.72, 44.84, 31.17, 28.71, 27.83, 10.27.

HRMS–FAB: m/z [M + Na]<sup>+</sup> calcd for C<sub>20</sub>H<sub>30</sub>NaO<sub>4</sub>: 357.2050; found: 357.2042.

# Benzyl (2RS,3RS,6SR,7SR)-3,6-Epoxy-8-hydroxy-7-iodo-2-methyloctanoate (17)

A 200-mL three-necked round-bottomed flask equipped with a magnetic stirrer bar, a  $N_2$  inlet adapter, and a septum was placed under a  $N_2$  atmosphere. The flask was charged with  $I_2$  (3.52 g, 13.9 mmol) and NaHCO<sub>3</sub> (2.33 g, 27.70 mmol) in anhyd MeCN (30 mL). After the suspension had been stirred for 15 min at 0 °C under  $N_2$ , a soln of **16** (925 mg, 2.77 mmol) in anhyd MeCN (8 mL) was added dropwise at -20 °C. After being stirred for 30 min, the reaction was quenched with sat. aq  $Na_2S_2O_3$  soln and brine, and the aqueous layer was extracted with EtOAc. The combined extract was washed with brine, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane–EtOAc, 3:1) to give **17**. This compound is unstable and was used in the next step without further purification.

Yield: 890 mg, 2.20 mmol (79%); pale yellow oil;  $R_f = 0.34$  (tolu-ene–EtOAc, 5:1).

<sup>1</sup>H NMR (300 MHz):  $\delta$  = 1.14 (d, *J* = 6.9 Hz, 3 H, 2-Me), 1.60–1.73 (m, 1 H), 1.81–2.05 (m, 2 H), 2.23 (dq, *J* = 12.7, 7.1 Hz, 1 H, 2-H), 2.53–2.65 (m, 1 H), 2.84–2.94 (dd, *J* = 8.0, 7.7 Hz, 1 H, OH), 3.81–3.88 (m, 2 H), 3.92–4.01 (m, 1 H, 3-H), 4.12–4.21 (dt, *J* = 8.8, 6.6 Hz, 2 H, 8-H), 5.10–5.14 (d, *J* = 12.6 Hz, 1 H, CHHPh), 5.15–5.19 (d, *J* = 12.6 Hz, 1 H, CHHPh), 7.27–7.43 (m, 5 H, Ph).

#### Benzyl (2*RS*,3*RS*,6*SR*)-3,6-Epoxy-8-hydroxy-2-methyloctanoate (18)

A 100-mL three-necked round-bottomed flask equipped with a magnetic stirrer bar, a N<sub>2</sub> inlet adapter, and a septum was placed under a N<sub>2</sub> atmosphere. The flask was charged with **17** (792 mg, 1.96 mmol) in anhyd CH<sub>2</sub>Cl<sub>2</sub> (20 mL). To this solution were added Bu<sub>3</sub>SnH (790  $\mu$ L, 2.94 mmol) and AIBN (33 mg, 0.2 mmol), and the mixture was stirred at r.t. for 6.5 h. The mixture was further stirred for 3 h after KF (ca. 100 mg) was added. The reaction mixture was filtered, and the filtrate was concentrated and chromatographed on silica gel (hexane–EtOAc, 3:1) to give **18**.

Yield: 477 mg, 1.71 mmol (87%); pale yellow oil;  $R_f = 0.21$  (hexane–EtOAc, 1:1).

IR (film): 3483 (w, OH), 2955 (m), 2944 (m), 2877 (m), 1734 (s, C=O), 1498 (w), 1457 (m), 1385 (w), 1254 (w), 1185 (m), 1058 (m), 739 (w), 698 (w) cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz): δ = 1.15 (d, J = 7.1 Hz, 3 H, 2-Me), 1.50–1.70 (m, 2 H, 4,5-H), 1.70–1.83 (m, 2 H, 7-H), 1.92–2.08 (m, 2 H, 4,5-H), 2.54–2.70 (m, 2 H, 2-H, OH), 3.74 (t, J = 5.5 Hz, 2 H, 8-H), 3.98–4.12 (m, 2 H, 3,6-H), 5.10–5.16 (d, J = 12 Hz, 1 H, CHHPh), 5.17–5.21 (d, J = 12 Hz, 1 H, CHHPh), 7.26–7.44 (m, 5 H, Ph).

<sup>13</sup>C NMR (75 MHz): δ = 174.69, 136.10, 128.54, 128.21, 128.16, 81.07, 79.46, 66.20, 61.27, 45.31, 37.61, 31.02, 28.65, 28.39, 13.27.

HRMS–FAB: m/z [M + H]<sup>+</sup> calcd for C<sub>16</sub>H<sub>23</sub>O<sub>4</sub>: 279.1598; found: 279.1597.

# Benzyl (2RS,3RS,6SR,8RS)-3,6-Epoxy-9,9,9-trifluoro-8-hydroxy-2-methylnonanoate (Benzyl $\omega$ -Trifluorononactate, 8) and 8-epi-8

A 200-mL three-necked round-bottomed flask equipped with a magnetic stirrer bar, a  $N_2$  inlet adapter, and a septum was placed under a  $N_2$  atmosphere. The flask was charged with Dess–Martin per-

iodinane (2.80 g, 6.54 mmol) in anhyd  $CH_2Cl_2$ . To this solution was added **18** (909 mg, 3.27 mmol) in anhyd  $CH_2Cl_2$  (10 mL) at 0 °C and the mixture was stirred for 2.5 h. The reaction mixture was poured into sat. aq  $Na_2S_2O_3$  soln and sat. aq  $NaHCO_3$  soln, and extracted with EtOAc. The combined extract was washed with brine, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure to give aldehyde **19**. This aldehyde is unstable and was used in the next step without further purification.

Yield: 933 mg; pale yellow oil.

<sup>1</sup>H NMR (300 MHz):  $\delta$  = 1.14 (d, *J* = 6.9 Hz, 3 H, 2-Me), 1.45–1.80 (m, 2 H), 1.91–2.20 (m, 2 H), 2.47–2.72 (m, 3 H), 4.09 (dt, *J* = 8.2, 7.2 Hz, 1 H, 3-H), 4.30 (pseudo quintet, *J* = 6.6 Hz, 1 H, 6-H), 5.09–5.14 (d, *J* = 12.4 Hz, 1 H, CHHPh), 5.16–5.20 (d, *J* = 12.4 Hz, 1 H, CHHPh), 7.22–7.42 (m, 5 H, Ph), 9.73 (t, *J* = 2.2 Hz, 1 H, 8-H).

A 200-mL three-necked round-bottomed flask equipped with a magnetic stirrer bar, a N<sub>2</sub> inlet adapter, and a septum was placed under a N<sub>2</sub> atmosphere. The flask was charged with **19** (933 mg, 3.38 mmol) in anhyd THF (65 mL). To this solution were added CF<sub>3</sub>TMS (0.750 mL, 5.07 mmol) and 1 M TBAF in THF (0.40 mL, 0.40 mmol) at 0 °C, and the mixture was stirred for 10 min. The mixture was further stirred for 15 min at 0 °C after 1 M aq HCl was added. The reaction mixture was poured into sat. aq NH<sub>4</sub>Cl soln and extracted with EtOAc. The combined extract was washed with brine, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane–EtOAc, 20:1) which gave **8** and 8-*epi*-**8**.

#### 8

Yield: 468 mg, 1.35 mmol (41% from **18**); pale yellow oil;  $R_f = 0.38$  (hexane–EtOAc, 1:1).

IR (film): 3434 (w, OH), 2955 (w), 2939 (w), 2870 (w), 1734 (s, C=O), 1498 (w), 1457 (w), 1385 (w), 1276 (s), 1163 (s), 1127 (s), 1072 (s), 860 (w), 739 (w), 698 (w), 575 (w) cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz):  $\delta$  = 1.15 (d, *J* = 7.1 Hz, 3 H, 2-Me), 1.52–1.82 (m, 3 H), 1.84–1.95 (m, 1 H), 1.96–2.10 (m, 2 H), 2.56 (quintet, *J* = 7.1 Hz, 1 H, 2-H), 3.38 (d, *J* = 5.5 Hz, 1 H, OH), 4.01–4.24 (m, 3 H, 3,6,8-H), 5.08–5.12 (d, *J* = 12 Hz, 1 H, CHHPh), 5.15–5.19 (d, *J* = 12 Hz, 1 H, CHHPh), 7.27–7.44 (m, 5 H, Ph).

<sup>13</sup>C NMR (75 MHz): δ = 174.63, 136.07, 128.58, 128.34, 128.25, 127.4 (q, *J* = 278 Hz, 9-C), 81.20, 75.40, 67.91 (q, *J* = 31.5 Hz, 8-C), 66.27, 45.44, 34.65, 30.63, 28.49, 13.42.

<sup>19</sup>F NMR (470 MHz):  $\delta = -80.599$  (d, J = 7.52 Hz).

HRMS–FAB:  $m/z [M + H]^+$  calcd for  $C_{17}H_{22}F_3O_4$ : 347.1470; found: 347.1470.

#### 8-epi-8

Yield: 496 mg, 1.43 mmol (44% from **18**); pale yellow oil;  $R_f = 0.41$  (hexane–EtOAc, 1:1).

<sup>1</sup>H NMR (300 MHz):  $\delta$  = 1.15 (d, *J* = 6.9 Hz, 3 H, 2-Me), 1.54–1.79 (m, 3 H), 1.90–2.15 (m, 3 H), 2.54–2.65 (quintet, *J* = 7.1 Hz, 1 H, 2-H), 4.05–4.17 (m, 3 H), 5.08–5.13 (d, *J* = 12.3 Hz, 1 H, CHHPh), 5.15–5.20 (d, *J* = 12.3 Hz, 1 H, CHHPh), 7.26–7.40 (m, 5 H, Ph).

MS (EI): *m*/*z* = 346 [M<sup>+</sup>], 255 [M – Bn]<sup>+</sup>, 237, 212, 194, 183, 170, 139, 122, 105, 91, 85, 55, 28.

HRMS (EI): m/z [M<sup>+</sup>] calcd for  $C_{17}H_{21}F_3O_4$ : 346.1392; found: 346.1395.

#### Conversion of 8-epi-8 into 8

A 30-mL two-necked round-bottomed flask equipped with a magnetic stirrer bar, a  $N_2$  inlet adapter, and a septum was placed under a  $N_2$  atmosphere. The flask was charged with 8-*epi*-8 (44 mg, 0.13 mmol), NMO (39 mg, 0.33 mmol), and 4 Å MS (30 mg) in anhyd CH<sub>2</sub>Cl<sub>2</sub> (2 mL). After TPAP (5 mg, 0.01 mmol) was added, the so-

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lution was stirred for 2.5 h at r.t. The reaction mixture was filtered through a Celite<sup>®</sup> pad and the filtrate was concentrated under reduced pressure to give **14**. This ketone was used in the next reduction step without further purification.

Yield: 26 mg; pale yellow oil;  $R_f = 0.34$  (toluene–EtOAc, 5:1).

A 30-mL two-necked round-bottomed flask equipped with a magnetic stirrer bar was charged with 14 (26 mg) in MeOH (2 mL). To this solution was added NaBH<sub>4</sub> (25 mg, 0.66 mmol) and the mixture was stirred for 30 min at r.t. Then, the reaction mixture was diluted with sat. aq NH<sub>4</sub>Cl soln and concentrated under reduced pressure. The residue was extracted with EtOAc and the combined extract was washed with brine, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane–EtOAc, 10:1) to give **8**.

Yield: 8.0 mg, 0.023 mmol (18%, two steps from 8-*epi*-**8**); pale yellow oil.

#### (+)-Benzyl (2*S*,3*S*,6*R*,8*S*)-8-[(2*S*)-2-Acetoxy-2-phenylacetoxy]-3,6-epoxy-9,9,9-trifluoro-2-methylnonanoate [(+)-20] and (+)-2,3,6,8-*epi*-20

A 50-mL three-necked round-bottomed flask equipped with a magnetic stirrer bar, a  $N_2$  inlet adapter, and a septum was placed under a  $N_2$  atmosphere. The flask was charged with **8** (300 mg, 0.867 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (18 mL). To this solution were added (*S*)-*o*-acetylmandelic acid (254 mg, 1.31 mmol), EDCI-HCl (250 mg, 1.31 mmol), and DMAP (12 mg, 0.1 mmol), and the mixture was stirred at r.t. for 1 h. The reaction mixture was poured into sat. aq NH<sub>4</sub>Cl soln and extracted with EtOAc. The combined extract was washed with brine, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane–EtOAc, 20:1) which gave (+)-**20** and (+)-2,3,6,8-*epi-***20**.

#### (+)-20

Yield: 226 mg, 0.433 mmol (quant); pale yellow oil;  $[a]_D^{24} + 16$  (*c* 0.27, CHCl<sub>3</sub>);  $R_f = 0.37$  (hexane–EtOAc, 3:1).

IR (film): 2979 (w), 2948 (w), 1776 (m, C=O), 1739 (s, C=O), 1497 (w), 1455 (w), 1375 (w), 1281 (w), 1231 (m), 1182 (m), 1062 (m), 739 (w), 698 (w) cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz):  $\delta$  = 1.12 (d, *J* = 7.2 Hz, 3 H, 2-Me), 1.40–1.70 (m, 2 H), 1.88 (t, *J* = 6.6 Hz, 2 H), 1.91–2.06 (m, 2 H), 2.20 (s, 3 H, Ac), 2.57 (quintet, *J* = 7.2 Hz, 1 H, 2-H), 3.85 (pseudo quintet, *J* = 6.5 Hz, 1 H, 3/6-H), 4.03 (pseudo q, *J* = 7.0 Hz, 1 H, 6/3-H), 5.10–5.14 (d, *J* = 12.6 Hz, 1 H, CHHPh), 5.15–5.19 (d, *J* = 12.6 Hz, 1 H, CHHPh), 5.50 (sextet, *J* = 6.5 Hz, 1 H, 8-H), 5.94 (s, 1 H, AcOCH), 7.25–7.46 (m, 10 H, 2 Ph).

<sup>13</sup>C NMR (75 MHz): δ = 172.14, 170.44, 167.37, 129.53, 128.86, 128.55, 128.24, 128.14, 127.59, 124.00 (q, *J* = 285 Hz, 9-C), 80.53, 75.85, 74.19, 74.11, 68.55 (q, *J* = 29 Hz, 8-C), 66.19, 45.21, 34.21, 30.97, 28.30, 20.47, 12.94.

<sup>19</sup>F NMR (470 MHz):  $\delta = -79.064$  (d, J = 6.11 Hz).

HRMS–FAB:  $m/z [M + H]^+$  calcd for  $C_{27}H_{30}F_3O_7$ : 523.1944; found: 523.1952.

#### (+)-2,3,6,8-epi-20

Yield: 223 mg, 0.427 mmol (99%); colorless crystals (recrystallized from hexane); mp 114–115 °C;  $[\alpha]_D^{24}$  +47 (*c* 0.51, CHCl<sub>3</sub>);  $R_f = 0.42$  (hexane–EtOAc, 3:1).

IR (film): 2951 (s), 2825 (s), 1781 (m, C=O), 1743 (s, C=O), 1382 (w), 1256 (m), 1188 (m), 1059 (s), 1033 (s), 800 (m) cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz):  $\delta$  = 1.07 (d, *J* = 6.6 Hz, 3 H, 2-Me), 1.14–1.28 (m, 2 H), 1.42–1.64 (m, 2 H), 1.67–1.76 (m, 2 H), 2.19 (s, 3 H, Ac), 2.48 (quintet, *J* = 7.4 Hz, 1 H, 2-H), 3.01 (quintet, *J* = 6.6 Hz, 1 H, 3/6-H), 3.74 (q, *J* = 7.2 Hz, 1 H, 6/3-H), 5.11–5.15 (d, *J* = 12.3 Hz,

1 H, CHHPh), 5.16–5.20 (d, J = 12.3 Hz, 1 H, CHHPh), 5.49 (sextet, J = 6.8 Hz, 1 H, 8-H), 5.98 (s, 1 H, AcOCH), 7.27–7.48 (m, 10 H, 2 Ph).

<sup>13</sup>C NMR (75 MHz): δ = 174.50, 170.21, 167.10, 136.22, 133.46, 129.50, 128.86, 128.57, 128.34, 128.17, 123.50 (q, *J* = 282 Hz, 9-C), 80.33, 74.06, 73.25, 68.29 (q, *J* = 33.2 Hz, 8-C), 66.27, 45.08, 33.71, 30.64, 28.15, 20.50, 12.95.

<sup>19</sup>F NMR (470 MHz):  $\delta$  = -78.807 (d, *J* = 6.11 Hz).

HRMS–FAB:  $m/z [M + H]^+$  calcd for  $C_{27}H_{30}F_3O_7$ : 523.1944; found: 523.1941.

#### X-ray Crystallographic Analysis of (+)-2,3,6,8-epi-20

Colorless crystals ( $C_{27}H_{29}F_3O_7$ ) were recrystallized from hexane, and the data were collected by using a Rigaku AFC7R diffractometer with Mo K $\alpha$  radiation and a rotating anode generator. Calculations were performed using the teXsan software package from Molecular Structure Corporation. The structure was solved by a direct method (SIR92) and expanded using Fourier techniques (DIRDIF94).

CCDC 823244 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data\_request/cif.

#### (-)-(2*S*,3*S*,6*R*,8*S*)-3,6-Epoxy-9,9,9-trifluoro-8-hydroxy-2-methylnonanoic Acid [ $\omega$ -Trifluorononactic Acid, (-)-2d]

A 100-mL one-necked round-bottomed flask equipped with a magnetic stirrer bar was charged with (+)-**20** (167 mg, 0.320 mmol) in MeOH (3 mL) and THF (4 mL). To this solution was added 1 M aq KOH (6 mL) at 0 °C and the mixture was stirred for 24 h. Then, the solvent was evaporated and the residue was washed with CHCl<sub>3</sub>. The aqueous layer was acidified with 1 M aq HCl and extracted with EtOAc. The combined extract was washed with brine, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure to give crude (-)-**2d** (135 mg) as a pale yellow oil. An analytical sample was further purified.

Colorless oil;  $[\alpha]_D^{24}$  –3.5 (*c* 0.71, CHCl<sub>3</sub>).

IR (film): 3415 (s, OH), 2962 (s), 1713 (s, C=O), 1277 (s), 1165 (s), 1128 (s), 1070 (s) cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz):  $\delta = 1.16$  (d, J = 6.8 Hz, 3 H, Me), 1.60–1.80 (m, 3 H, 4,5-H), 1.88 (ddd, J = 13.5, 10.1, 3.0 Hz, 1 H), 2.00–2.20 (m, 2 H, 7-H), 2.46 (quintet, J = 6.8 Hz, 1 H, 2-H), 4.00–4.13 (m, 1 H), 4.14–4.40 (m, 2 H), 5.9–7.2 (br, 1 H, CO<sub>2</sub>H).

<sup>13</sup>C NMR (151 MHz): δ = 179.53, 125.31 (q, J = 282 Hz, 9-C), 81.59, 75.16, 67.22 (q, J = 31.4 Hz, 8-C), 46.34, 35.21, 30.72, 29.00, 13.78.

<sup>19</sup>F NMR (470 MHz):  $\delta = -80.901$  (d, J = 10.8 Hz).

HRMS–FAB:  $m/z [M + H]^+$  calcd for  $C_{10}H_{16}F_3O_4$ : 257.1000; found: 257.1004.

#### (-)-8

A 50-mL two-necked round-bottomed flask equipped with a magnetic stirrer bar, a  $N_2$  inlet adapter, and a septum was placed under a  $N_2$  atmosphere. The flask was charged with *t*-BuOK (119 mg, 1.06 mmol) in anhyd DMF (10 mL). To this solution was added the crude (–)-**2d** in anhyd DMF (2 mL) and the mixture was then warmed to 60 °C and stirred for 5 min. To this was added BnBr (126  $\mu$ L, 1.06 mmol) and the solution was stirred for 16 h. The reaction mixture was diluted with EtOAc, and washed with H<sub>2</sub>O and brine. The organic layer was dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane–EtOAc, 10:1) to give (–)-**8**.

Yield: 77 mg, 0.22 mmol (70%); pale yellow oil;  $[\alpha]_{D}^{24}$  –0.45 (*c* 0.55, CHCl<sub>3</sub>).

MS (EI):  $m/z = 346 \text{ [M^+]}$ , 255 [M – Bn]<sup>+</sup>, 237, 212, 194, 183, 170, 139, 107, 91, 85, 83, 55, 43.

HRMS (EI): m/z [M<sup>+</sup>] calcd for  $C_{17}H_{21}F_3O_4$ : 346.1392; found: 346.1390.

#### (+)-2d

A 30-mL one-necked round-bottomed flask equipped with a magnetic stirrer bar was charged with (+)-2,3,6,8-*epi*-**20** (90 mg, 0.17 mmol) in MeOH (1 mL) and THF (3 mL). To this solution was added 1 M aq KOH (4 mL) at 0 °C and the mixture was stirred for 24 h. Then, the solvent was evaporated and the residue was washed with CHCl<sub>3</sub>. The aqueous layer was acidified with 1 M HCl and extracted with EtOAc. The combined extract was washed with brine, dried (MgSO<sub>4</sub>), and concentrated under reduced pressure to give crude (+)-**2d** (71 mg) as a pale yellow oil. This carboxylic acid was used in the next step without further purification. An analytical sample was further purified.

Colorless oil;  $[\alpha]_{D}^{24}$  +3.3 (*c* 0.50, CHCl<sub>3</sub>).

HRMS–FAB:  $m/z [M + H]^+$  calcd for  $C_{10}H_{16}F_3O_4$ : 257.1000; found: 257.0999.

#### (+)-8

A 50-mL two-necked round-bottomed flask equipped with a magnetic stirrer bar, a  $N_2$  inlet adapter, and a septum was placed under a  $N_2$  atmosphere. The flask was charged with *t*-BuOK (63 mg, 0.56 mmol) in anhyd DMF (6 mL). To this solution was added the crude (+)-**2d** in anhyd DMF (2 mL) and the mixture was then warmed to 60 °C and stirred for 5 min. To this was added BnBr (70  $\mu$ L, 0.59 mmol) and the mixture was stirred for 20 h. The reaction mixture was diluted with EtOAc, and washed with H<sub>2</sub>O and brine. The organic layer was dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane–EtOAc, 10:1) to give (+)-**8**.

Yield: 55 mg, 0.16 mmol (92%); pale yellow oil;  $[\alpha]_{D}^{24}$  +0.56 (*c* 0.90, CHCl<sub>3</sub>).

HRMS–FAB:  $m/z [M + H]^+$  calcd for  $C_{17}H_{22}F_3O_4$ : 347.1469; found: 347.1472.

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