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SYNTHESIS OF A CAGE-ANNULATED DITOPIC RECEPTOR

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Abstract - The synthesis of a cage-annulated ditopic receptor (**2**) is described along with that of a corresponding model compound (**3**). Compound (**2**) is designed for use as a host system for selective complexation and transport of NaOH from aqueous alkaline media into organic media.

INTRODUCTION

There is considerable current interest in the synthesis of crown ethers and cryptands that serve as host molecules for highly selective complexation and transport of cationic and anionic species.[1] Recently, the syntheses of several new cage annulated crown ethers and cryptands have been reported, and their ability to function as a new class of metal cation complexants has been evaluated.[2]

In molecules of this type, the cage moiety functions as a rigidifying spacer that lowers the conformational mobility of the host molecule and also affects the size and shape of the host cavity relative to the corresponding non-cage annulated system. In addition, the cage moiety is highly lipophilic, and its incorporation into the host system aids in recovery when metal cation guests are complexed and transported from aqueous media into an organic phase.

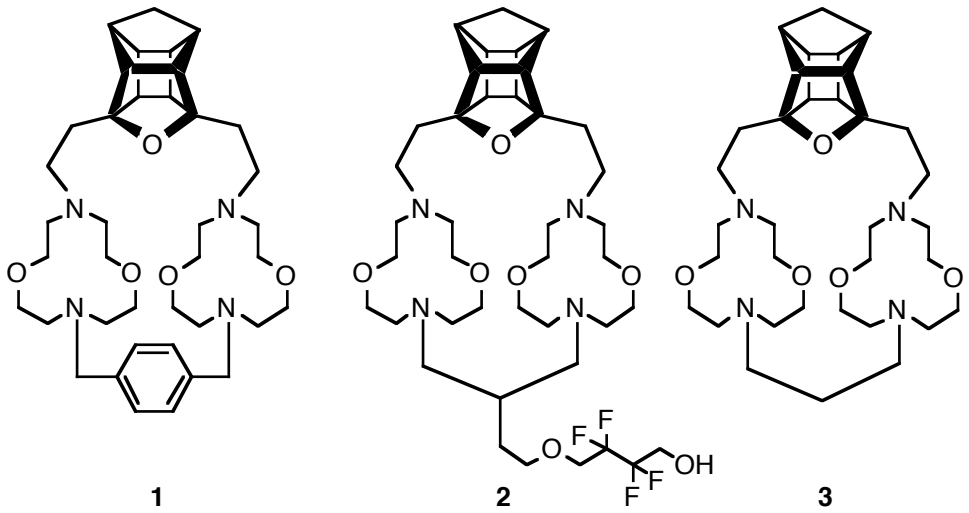
An important current application of cage annulated host systems involves their use as selective complexants for removal of NaOH from alkaline tank wastes stored at various U. S. Department of Energy sites.[3] In particular, host systems of this type have been employed as metal cation receptors in synergistic combination with proton-ionizable fluorinated alcohols to promote pseudo-hydroxide extraction.[3,4]

Recently, *ditopic receptors* have been prepared that are capable of simultaneous selective complexation of *both* cationic and anionic species.[5] The objective of the present study is to prepare cage annulated crown ethers to which a pendant proton-ionizable fluorinated alcohol moiety has been attached. It is anticipated that the resulting proton-ionizable lariat crown ether[6] will function as a selective ditopic

receptor for selective extraction of Na^+ and psuedo-extraction of hydroxide anion from aqueous alkaline media. In addition, attachment of the proton-ionizable alcohol moiety to the crown ether may foster a stablizing elelctrostatic interaction between the host-Na^+ complex and the O^- "tail" at one terminus of the lariat moiety.

RESULTS AND DISCUSSION

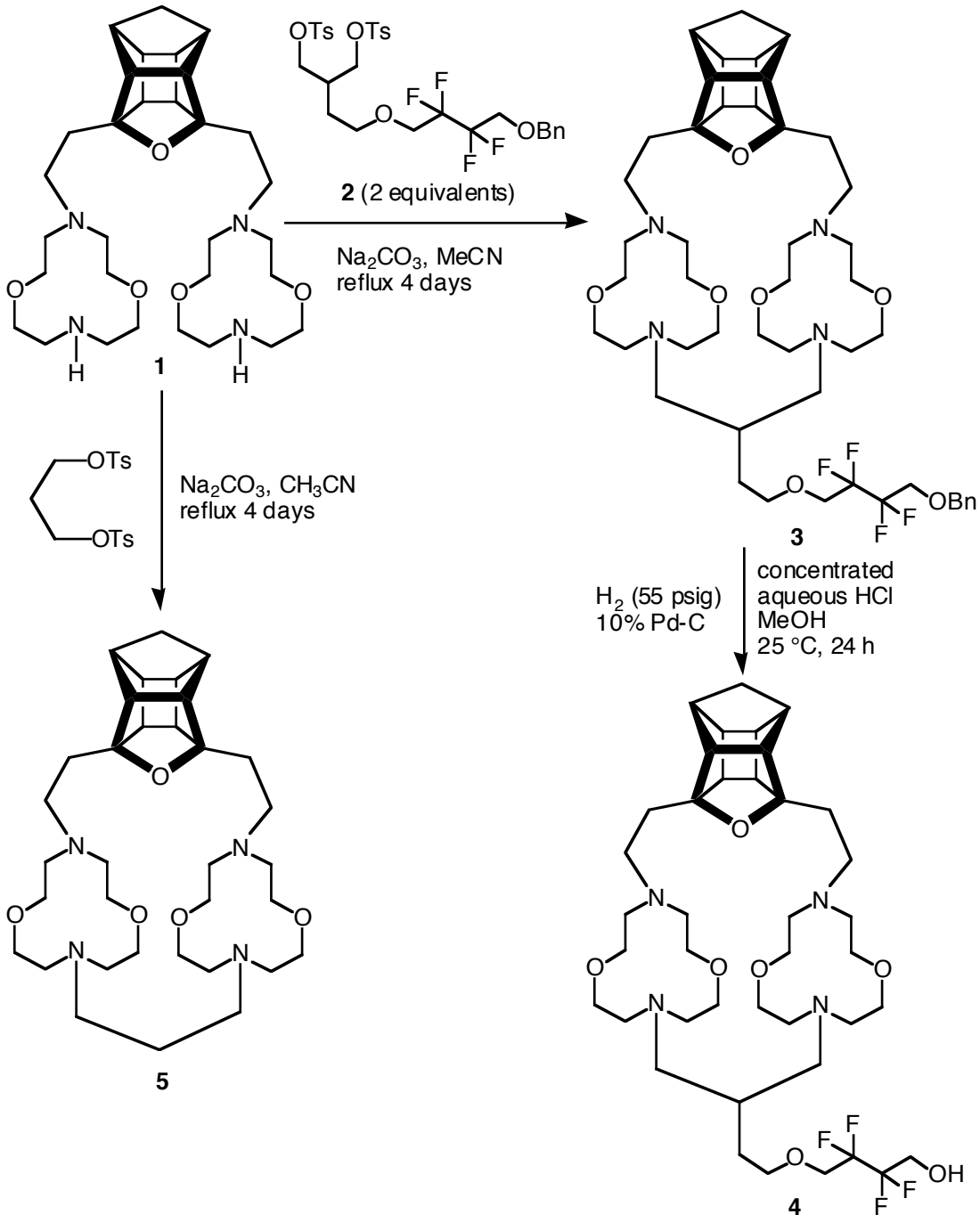
In 1998, we reported the synthesis and alkali metal picrate extraction profile of a novel, cage-annulated bis(1,7-diaza-12-crown-4) ether, i.e., **1** (Scheme 1).[7] This host molecule proved to be an efficient Na^+ complexant, a result that reflects the high level of host preorganization attendant with its "molecular box" configuration. In the present study, we have focused our attention upon an analogous host system (**2**) (Scheme 1), that takes advantage of the forced cooperativity between the bis(1,7-diaza-12-crown-4) ether moieties in system (**1**) and that also provides a proton-ionizable alcohol lariat.



Scheme 1.

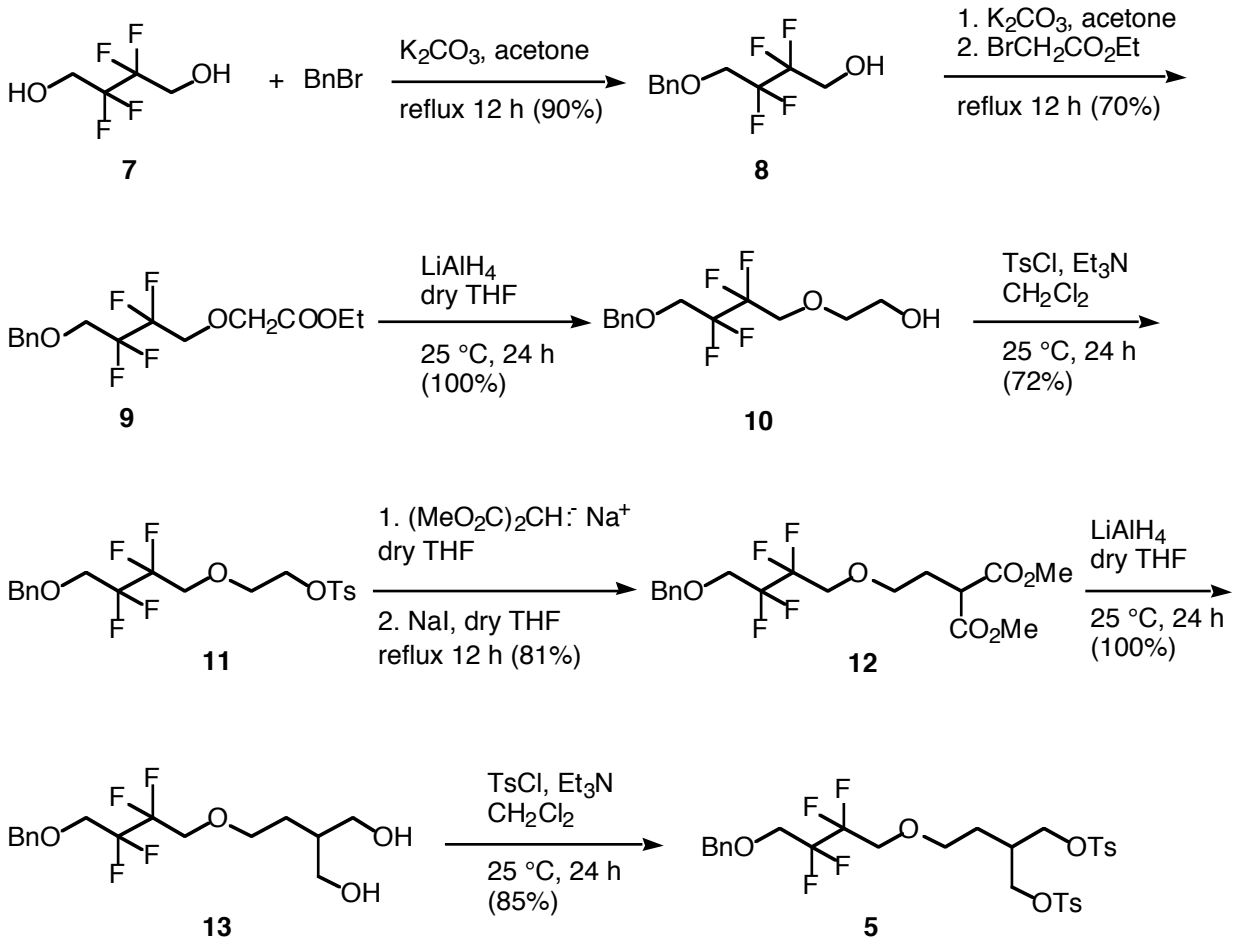
Based upon our prior experience with host system (**1**)[7] and with the synergistic effects that fluorinated alcohols exert upon the NaOH extracting ability of cage-annulated crown ethers,[3,4] we anticipate that **2** may function effectively as an effective NaOH extractant. In addition, we have designed a model system (**3**), which embodies the fundamental "molecular box" features of **2**, but which lacks the proton-ionizable alcohol lariat moiety.

The method used to prepare cage annulated podand (**4**) has been described previously.[7] This compound was converted into the corresponding cage annulated molecular boxes (**2**) and (**3**) by using the approach outlined in Scheme 2.



Scheme 2

In order to synthesize host system (**2**), it was necessary to prepare an appropriately functionalized "connector" (**5**) (Scheme 2), that contains the required fluorinated alcohol lariat moiety. The procedure that was employed for this purpose is shown in Scheme 3. Subsequent attachment of **5** to **4** produced cage annulated lariat crown ether **6**. This was followed by catalytic hydrogenolysis of the O-CH_2Ph bond in **6**, thereby affording the desired host system (**2**) in moderate overall yield.



Scheme 3.

EXPERIMENTAL

Melting points are uncorrected. Proton and ^{13}C NMR spectra were obtained at 200 MHz and at 50 Mz, respectively by using a Varian Gemini 200 NMR spectrometer. HRMS spectral data reported herein were obtained by personnel at the Mass Spectrometry Facility at the Department of Chemistry and Biochemistry, University of Texas at Austin by using a ZAB-E double sector high-resolution mass spectrometer (Micromass, Manchester, England) that was operated in the chemical ionization mode.

Synthesis of 6. A mixture of **4**[7] (560 mg, 1.0 mmol), **5** (*vide infr*a, 662 mg, 1.0 mmol), and Na_2CO_3 (1.05 g, 10 mmol) in MeCN (150 mL) was refluxed with stirring during 4 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered. The residue was washed with CH_2Cl_2 (30 mL), and the combined filtrates were concentrated *in vacuo*. The residue was purified *via* column chromatography on basic alumina by using a 10-20% MeOH-EtOAc gradient elution scheme.

Pure **6** (590 mg, 68%) was thereby obtained as a colorless oil; IR (KBr) 2945 (s), 2854 (s), 2234 (w), 1454 (s), 1356 (m), 1291 (m), 1112 (s), 911 (m), 732 cm^{-1} (s); ^1H NMR ($CDCl_3$) □1.45-1.70 (m, 4 H), 1.78-1.95 (m, 6 H), 2.24-2.62 (m, 27 H), 3.50-3.95 (m, 26 H), 4.64 (s, 2 H), 7.30 (s, 5 H)**;** ^{13}C NMR ($CDCl_3$) □30.2 (t), 30.3 (t), 31.0 (t), 31.1 (t), 32.4 (d), 32.5 (d), 41.4 (d), 41.6 (d), 43.5 (t), 43.6 (t), 44.1 (d), 44.4 (d), 47.1 (d), 48.9 (d), 52.5 (t), 53.1 (t), 54.9 (t), 55.0 (t), 55.4 (t), 56.0 (t), 57.8 (d), 59.4 (d), 60.3 (t), 67.7 (t, $^2J_{CF}$ = 25.0 Hz) 67.9 (t, $^2J_{CF}$ = 25.0 Hz), 69.0 (t), 69.3 (t), 71.4 (t), 74.3 (t), 94.9 (s), 95.0 (s), 116.8 (tt, $^1J_{CF}$ = 253.1 Hz, $^2J_{CF}$ = 31.0 Hz), 127.7 (d), 128.0 (d), 128.5 (d), 136.8 (s). Exact MS: $[M_r + 1]^+$ calcd for $C_{47}H_{70}N_4O_7F_4$, *m/z* 879.5259. Found (high-resolution chemical ionization mass spectrometry): *m/z* 879.5245.

Synthesis of Cage-annulated Ditopic Receptor (2). To a solution of **6** (220 mg, 0.25 mmol) in MeOH (25 mL) was added concentrated aqueous HCl (0.5 mL) and 10% palladized charcoal (100 mg, catalytic amount). The resulting mixture was subjected to hydrogenolysis on a Parr shaker apparatus at 55 psig at ambient temperature during 24 h. The reaction mixture was filtered to remove spent catalyst, and the filtrate was concentrated *in vacuo*. The residue was neutralized *via* careful, dropwise addition of concentrated aqueous NH_4OH (*ca.* 5 mL), and CH_2Cl_2 (60 mL) then was added to the resulting aqueous suspension. The layers were separated; the organic layer was dried (anhydrous K_2CO_3) and filtered, and the filtrate was concentrated *in vacuo*. Pure **6** (180 mg, 90%) was thereby obtained as a colorless, viscous oil; IR (KBr) 3290 (br, w), 2950 (s), 2861 (s), 1452 (m), 1357 (m), 1295 (m), 1125 (s), 911 (m), 732 cm^{-1} (s); ^1H NMR ($CDCl_3$) □1.42-1.53 (m, 4 H), 1.75-2.20 (m, 6 H), 2.27-2.84 (m, 28 H), 3.32-4.70 (m, 26 H); ^{13}C NMR ($CDCl_3$) □30.3 (t), 31.0 (t), 31.1 (t), 32.4 (t), 32.5 (t), 41.4 (d), 41.6 (d), 43.5 (t), 43.6 (t), 44.1 (d), 44.3 (d), 47.1 (d), 48.7 (d), 52.6 (t), 53.0 (t), 54.7 (t), 56.0 (t), 55.4 (t), 55.7 (t), 57.9 (d), 59.3 (d), 60.6 (t), 68.0 (t, $^2J_{CF}$ = 29.6 Hz), 69.0 (t, $^2J_{CF}$ = 29.6 Hz), 69.2 (t), 69.5 (t), 70.8 (t), 94.90 (s), 95.0 (s), 116.2 (tt, $^1J_{CF}$ = 251.5 Hz, $^2J_{CF}$= 31.5 Hz). Exact MS: $[M_r + 1]^+$ calcd for $C_{40}H_{64}N_4O_7F_4$, *m/z* 789.4789 Found (high-resolution chemical ionization mass spectrometry): *m/z* 789.4795.

Synthesis of Model System (3). A mixture of **4**[7] (150 mg, 0.27 mmol), 1,3-propanediol ditosylate (103 mg, 0.27 mmol), and Na_2CO_3 (318 mg, 2.7 mmol) in CH_3CN (25 mL) was refluxed with stirring during 4 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered. The residue was washed with CH_2Cl_2 (30 mL), and the combined filtrates were concentrated *in vacuo*. The residue was purified via column chromatography on basic alumina by using a 10-20% MeOH-EtOAc

gradient elution scheme. Pure **3** (100 mg, 64%) was thereby obtained as a colorless oil; IR (KBr) 2942 (s), 2851 (s), 1451 (m), 1356 (m), 1124 (s), 915 (m) 729 cm^{-1} (s); ^1H NMR ($CDCl_3$) □1.47 (d, J = 12.0 Hz, 1 H), 1.52-1.67 (m, 2 H)1.78-1.95 (m, 5 H), 2.34 (s, 2 H), 2.49-2.80 (m, 30 H), 3.55 (t, J = 8.0 Hz, 8 H), 3.65 (t, J = 8.0 Hz, 8 H); ^{13}C NMR ($CDCl_3$) □24.9 (t), 30.3 (t), 41.4 (d), 43.5 (t), 44.1 (d), 47.7 (d), 52.4 (t), 54.4 (t), 54.8 (t), 55.0 (t), 58.6 (d), 69.1 (t), 69.5 (t), 94.9 (s). Exact MS: $[M_r + 1]^+$ calcd for $C_{34}H_{56}N_4O_5$, *m/z* 601.4329. Found (high-resolution chemical ionization mass spectrometry): *m/z* 600.4341.

Mono-*O*-benzyl-2,2,3,3-tetrafluorobutane-1,4-diol (8). A mixture of 2,2,3,3-tetrafluoro-1,4-butanediol (**7**, 4.05 g, 25 mmol), benzyl bromide (3.0 mL, 25 mmol), and anhydrous K_2CO_3 (17.3 g, 125 mmol) in dry acetone (200 mL) was refluxed with stirring during 12 h. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered. The filtrate was concentrated *in vacuo*, thereby affording **8** (5.6 g, 90%) as a colorless oil. This material was used as obtained in the next step without additional purification; IR (film) 3423 (br, m), 3040 (w), 2943 (m), 1455 (s), 1184 (m), 1119 (s), 1027 (m), 747 (s), 699 cm^{-1} (s); ^1H NMR ($CDCl_3$) □2.65 (br s, 1 H), 3.87 (t, J = 13.2 Hz, 2 H), 4.0 (dt, J_1 = 13.2 Hz, J_2 = 7.5 Hz, 2 H), 4.65 (s, 2 H), 7.25-7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$) □60.6 (t, $^2J_{CF}$ = 27.1 Hz), 66.8 (t, $^2J_{CF}$ = 27.9 Hz), 74.6 (t), 116.5 (tt, $^1J_{CF}$ = 251.4 Hz, $^2J_{CF}$ = 30.1 Hz), 116.6 (tt, $^1J_{CF}$ = 252.0 Hz, $^2J_{CF}$ = 30.8 Hz), 128.4 (d), 128.9 (d), 129.1 (d), 136.6 (s). Exact mass: $[M_r + 1]^+$ calcd for $C_{11}H_{12}O_2F_4$, *m/z* 253.0847. Found (high-resolution chemical ionization mass spectrometry): *m/z* 253.0852.

***O*-Benzyl-*O*'-ethoxycarbonylmethyl-2,2,3,3-tetrafluorobutane-1,4-diol (9).** A mixture of **8** (5.6 g, 22 mmol), ethyl bromoacetate (2.5 mL, 22 mmol), and anhydrous K_2CO_3 (15.2 g, 110 mmol) in dry acetone (200 mL) was refluxed with stirring during 24 h. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered. The filtrate was concentrated *in vacuo*, and the residue was purified via column chromatography on silica gel by using a 7-10% EtOAc-hexane gradient elution scheme. Pure **9** (5.3 g, 70%) was thereby obtained as a colorless oil; IR (film) 3091(w), 3065 (w), 3034 (m), 2984 (s), 2937 (s), 2887 (s), 1753 (s), 1497 (m), 1455 (s), 1378 (s), 1280 (s), 1216 (m), 1132 (s), 1029(s), 954 (s), 929 (s), 741 (m), 691 (s), 668 cm^{-1} (m); ^1H NMR ($CDCl_3$) □1.26 (t, J = 7.1 Hz, 3 H), 3.87 (tt, $^1J_{HF}$ = 17.5 Hz, $^2J_{HF}$ = 1.6 Hz, 2 H), 4.03 (tt, $^1J_{HF}$ = 17.5 Hz, $^2J_{HF}$ = 1.6 Hz, 2 H), 4.17 (s, 2 H), 4.19 (q, J = 7.1 Hz, 2 H), 4.62 (s, 2H), 7.32 (s, 5H); ^{13}C NMR ($CDCl_3$) □14.1 (q), 61.1 (t), 66.7 (t, $^2J_{CF}$ =

25.5 Hz, $\underline{C}H_2CF_2$), 68.2 (t, $^2J_{CF}$ = 25.5 Hz, $\underline{C}H_2CF_2$), 69.2 (t), 74.3 (t), 115.96 (tt, $^1J_{CF}$ = 267.5 Hz, $^2J_{CF}$ = 31.5 Hz, $\underline{C}F_2$), 116.14 (tt, $^1J_{CF}$ = 267.5 Hz, $^2J_{CF}$ = 31.5 Hz, $\underline{C}F_2$), 127.8 (d), 128.1 (d), 128.5 (d), 138.4 (s), 169.4 (s). Exact MS: $[M_r + 1]^+$ calcd for $C_{15}H_{18}O_4F_4$, *m/z* 339.1219. Found (high-resolution chemical ionization mass spectrometry): *m/z* 339.1225.

***O*-Benzyl-*O'*-(2'-hydroxyethyl)-2,2,3,3-tetrafluorobutane-1,4-diol (10).** To a suspension of $LiAlH_4$ (1.14 g, 30 mmol) in dry THF (60 mL) under nitrogen at ambient temperature was added dropwise with stirring a solution of **9** (5.25 g, 15.5 mmol) in dry THF (10 mL) during 0.5 h. After the addition of reagents had been completed, the resulting mixture was stirred at ambient temperature during 24 h. The stirred reaction mixture was cooled to 0 °C *via* application of an external ice-water bath, and excess $LiAlH_4$ was quenched *via* careful, dropwise addition of water (30 mL). The resulting aqueous suspension was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed sequentially with water (25 mL) and brine (20 mL), dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. Compound (**10**) (4.5 g, 100%) was thereby obtained as a colorless oil. This material was used as obtained in the next step without additional purification; IR (film) 3454 (s), 3038 (s), 2984 (s), 2940 (s), 2882 (s), 1455 (s), 1370 (m), 1246 (m), 1180 (m), 1127 (s), 953 (m), 929 (s), 780 (w), 742 (m), 699 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 3.68 (br s, 4 H), 3.88 (t, *J* = 12.2 Hz, 2 H), 3.94 (t, *J* = 12.2 Hz, 2 H), 4.64 (s, 2 H), 7.33 (s, 5 H); ^{13}C NMR ($CDCl_3$) δ 61.1 (t), 66.7 (t, $^2J_{CF}$ = 25.4 Hz, $\underline{C}H_2CF_2$), 68.1 (t, $^2J_{CF}$ = 25.4 Hz, $\underline{C}H_2CF_2$), 74.1 (t), 74.4 (t), 116.18 (tt, $^1J_{CF}$ = 252.5 Hz, $^2J_{CF}$ = 30.2 Hz, $\underline{C}F_2$), 116.22 (tt, $^1J_{CF}$ = 252.5 Hz, $^2J_{CF}$ = 30.2 Hz, $\underline{C}F_2$), 127.9 (d), 128.2 (d), 128.5 (d), 136.7 (s). Exact MS: $[M_r + 1]^+$ calcd for $C_{13}H_{16}F_4O_3$, *m/z* 297.1114. Found (high-resolution chemical ionization mass spectrometry): *m/z* 297.1109.

***O*-Benzyl-*O'*-(2'-*p*-toluenesulfonyloxyethyl)-2,2,3,3-tetrafluorobutane-1,4-diol (11).** To a solution of **10** (6.96 g. 23.5 mmol) and Et_3N (7.0 mL, 50 mmol) in CH_2Cl_2 (150 mL) at ambient temperature was added portionwise with stirring *p*-toluenesulfonyl chloride (7.2 g, 38 mmol). After all of the reagents had been added, the resulting mixture was stirred at ambient temperature during 24 h. The resulting mixture was washed sequentially with water (2 × 40 mL) and brine (20 mL), dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by using a 6-9% EtOAc-hexane gradient elution scheme. Pure **11** (7.6 g, 72%) was thereby obtained as a colorless, viscous oil; IR (film) 3066 (s), 3033 (m), 2930 (s), 2882 (s), 1598 (s), 1498 (m), 1460 (s), 1370

(m), 1302 (m), 1293 (m), 1190 (s), 1127 (s), 1020 (s), 950 (s), 816 (s), 775 (w), 748 (m), 699 (s), 663 cm^{-1} (s); ^1H NMR ($CDCl_3$) □2.43 (s, 3 H), 3.74 – 3.95 (m, 6 H), 4.14 (t, J = 4.5 Hz, 2 H), 4.64 (s, 2 H), 7.30 – 7.35 (m, 7 H), 7.78 (A*B*, J_{AB} = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) □21.4 (q), 66.7 (t, $^2J_{CF}$ = 25.5 Hz, $\underline{C}H_2CF_2$), 68.2 (t, $^2J_{CF}$ = 25.5 Hz, $\underline{C}H_2CF_2$), 68.8 (t), 70.1 (t), 74.2 (t), 115.96 (tt, $^1J_{CF}$ = 252.0 Hz, $^2J_{CF}$ = 31.0 Hz, $\underline{C}F_2$), 116.07 (tt, $^1J_{CF}$ = 252.0 Hz, $^2J_{CF}$ = 31.0 Hz, $\underline{C}F_2$), 127.8 (d), 127.9 (d), 128.1 (d), 128.5 (d), 129.8 (d), 132.7 (s), 136.7 (s), 145.0 (s). Exact MS: $[M_r + 1]^+$ calcd for $C_{20}H_{22}O_5SF_4$, *m/z* 451.1202. Found (high-resolution chemical ionization mass spectrometry): *m/z* 451.1189.

Preparation of 12. A solution of sodium dimethylmalonate in dry THF was prepared by reacting dimethyl malonate (4.0 mL, 35 mmol) and NaH (obtained as a 60% dispersion in mineral oil, 0.8 g, 33 mmol) in dry THF (80 mL). To the resulting solution was added dropwise with stirring a solution of **11** (7.1 g, 16 mmol) and NaI (600 mg, 4.0 mmol) in dry THF (50 mL). After all of the reagents had been added, the resulting mixture was refluxed overnight. The reaction mixture then was allowed to cool gradually to ambient temperature and was quenched via careful, dropwise addition with stirring of water (40 mL). The resulting aqueous suspension was extracted with Et_2O (100 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 □ 70 mL). The combined organic extracts were washed sequentially with water and brine, dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by using a 10-15% EtOAc-hexane gradient elution scheme. Pure **12** (5.3 g, 81%) was thereby obtained as a colorless oil; IR (film) 3104 (w), 3069 (s), 2956 (s), 2898 (s), 1753 (s), 1738 (s), 1454 (s), 1439 (s), 1342 (s), 1243 (s), 1199 (s), 1133 (s), 1045 (s), 1038 (s), 933 (s), 745 (m), 699 cm^{-1} (s); ^1H NMR ($CDCl_3$) □2.17 (q, J = 7.5 Hz, 2 H), 3.55 – 3.63 (m, 3 H), 3.71 (s, 6 H), 3.78 – 3.95 (m, 4 H), 4.63 (s, 2 H), 7.32 (br s, 5 H); ^{13}C NMR ($CDCl_3$) □28.8 (t), 48.3 (d), 52.5 (q), 66.7 (t, $^2J_{CF}$ = 25.5 Hz, $\underline{C}H_2CF_2$), 67.8 (t, $^2J_{CF}$ = 25.5 Hz, $\underline{C}H_2CF_2$), 70.0 (t), 74.3 (t), 116.12 (tt, $^1J_{CF}$ = 252.0 Hz, $^2J_{CF}$ = 31.2 Hz, $\underline{C}F_2$), 116.19 (tt, $^1J_{CF}$ = 252.0 Hz, $^2J_{CF}$ = 31.2 Hz, $\underline{C}F_2$), 127.8 (d), 128.1 (d), 128.5 (d), 136.7 (s), 169.6 (s). Exact MS: $[M_r + 1]^+$ calcd for $C_{18}H_{22}O_5F_4$, *m/z* 411.1431. Found (high-resolution chemical ionization mass spectrometry): *m/z* 411.1416.

Lithium Aluminum Hydride Promoted Reduction of 12. To a suspension of $LiAlH_4$ (1.87 g, 50 mmol) in dry THF (60 mL) at ambient temperature was added dropwise with stirring a solution of **12** (5.00 g, 12.2 mmol) in dry THF (80 mL). After all of the reagents had been added, the resulting mixture was stirred at ambient temperature during 24 h. The stirred reaction mixture was cooled to 0 °C *via*

application of an external ice-water bath, and excess $LiAlH_4$ was quenched *via* careful, dropwise addition of water (30 mL). The resulting aqueous suspension was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed sequentially with water (30 mL) and brine (25 mL), dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. Compound (**13**) (4.2 g, 100%) was thereby obtained as a colorless oil. This material was used as obtained in the next step without additional purification; IR (film) 3430 (m), 3030 (s), 2933 (s), 2892 (s), 1463 (s), 1377 (s), 1282 (s), 1243 (s), 1189 (s), 1127 (s), 1035 (s), 961 (s), 745 (s), 699 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.62 (q, J = 6.3 Hz, 2 H), 1.70-1.90 (m, 1 H), 2.85 (br s, 2 H), 3.60 –3.71 (m, 6 H), 3.79 – 3.94 (m, 4 H), 4.63 (s, 2 H), 7.33 (br s, 5 H); ^{13}C NMR ($CDCl_3$) δ 27.9 (t), 39.8 (d), 65.1 (t), 66.1 (t, $^2J_{CF}$ = 25.4 Hz, $\underline{C}H_2CF_2$), 67.8 (t, $^2J_{CF}$ = 25.4 Hz, $\underline{C}H_2CF_2$), 71.1 (t), 74.3 (t), 116.11 (tt, $^1J_{CF}$ = 251.5 Hz, $^2J_{CF}$ = 31.3 Hz, $\underline{C}F_2$), 116.18 (tt, $^1J_{CF}$ = 251.5 Hz, $^2J_{CF}$ = 31.3 Hz, $\underline{C}F_2$), 127.8 (d), 128.1 (d), 128.5 (d), 136.7 (s). Exact MS: $[M_r + 1]^+$ calcd for $C_{16}H_{22}O_4F_4$, *m/z* 355.1532. Found (high-resolution chemical ionization mass spectrometry): *m/z* 355.1534.

Preparation of 5. To a solution of **13** (1.75 g, 5.00 mmol) and NEt_3 (4.2 mL, 30 mmol) in CH_2Cl_2 (70 mL) at ambient temperature was added portionwise with stirring *p*-toluenesulfonyl chloride (3.9 g, 20 mmol). After all of the reagents had been added, the reaction mixture was stirred at ambient temperature during 24 h. The resulting mixture was washed sequentially with water (2 × 30 mL) and brine (20 mL), dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified *via* column chromatography on silica gel by using a 30-40% EtOAc-hexane gradient elution scheme. Pure **5** (2.8 g, 85%) was thereby obtained as a colorless microcrystalline solid: mp 44-45 °C; IR (film) 3067 (m), 3033 (m), 2928 (s), 2835 (s), 1597 (s), 1495 (m), 1455 (s), 1362 (s), 1241 (m), 1211 (m), 1177 (s), 1130 (s), 1097 (s), 973 (s), 949 (s), 816 (s), 786 (s), 737 (m), 695 (m), 667 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.55 (q, J = 6.3 Hz, 2 H), 2.12 - 2.22 (m, 1 H), 2.42 (m, 6 H), 3.46 (t, J = 4.6 Hz, 8 H), 3.41 (t, J = 6.5 Hz, 8 H), 4.62 (s, 2 H), 7.29 – 7.34 (m, 9 H), 7.72 (A*B*, J_{AB} = 8.3 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 21.6 (q), 27.0 (t), 35.2 (d), 66.5 (t, $^2J_{CF}$ = 27.5 Hz, $\underline{C}H_2CF_2$), 67.7 (t, $^2J_{CF}$ = 27.5 Hz, $\underline{C}H_2CF_2$), 68.6 (t), 69.4 (t), 74.2 (t), 115.93 (tt, $^1J_{CF}$ = 252.1 Hz, $^2J_{CF}$ = 30.7 Hz, $\underline{C}F_2$), 116.02 (tt, $^1J_{CF}$ = 252.0 Hz, $^2J_{CF}$ = 30.8 Hz, $\underline{C}F_2$), 127.8 (d), 128.1 (d), 128.5 (d), 129.9 (d), 132.3 (s), 136.6 (s), 145.1 (s). Exact MS: $[M_r + 1]^+$ calcd for $C_{30}H_{34}F_4O_8S_2$, *m/z* 663.1710. Found (high-resolution chemical ionization mass spectrometry): *m/z* 663.1685.

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